THE CIRCULATORY RESPONSE TO INTRAVENOUS ERGOMETRINE IN ANAESTHETIZED PARTURIENT WOMEN

by

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PREFACE.

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Thomas W. Baillie.

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GENERAL INTRODUCTION.

The years that have passed since the end of World War II have brought many outstanding changes in the practice of anaesthesia. Of the alterations that have taken place, one of the most obvious has surely been the displacement of vasodepressant agents such as di-ethyl ether and chloroform by the nitrous oxide: oxygen: muscle relaxant sequence with endotracheal intubation and intermittent positive-pressure ventilation of the lungs. This latter method, by virtue of its safety, relatively pleasant and rapid recovery, non-flammability and provision of good operating conditions for anaesthetist and surgeon alike, has come to enjoy almost universal adoption as the anaesthetic technique of choice for a wide variety of surgical procedures. In obstetrical anaesthesia in particular, the marked absence of respiratory depression of the newborn when compared with di-ethyl ether, chloroform, trichlorethylene and trimethylene (cyclopropane), elects the nitrous oxide: oxygen: muscle relaxant sequence as the usual method of choice.

Such modern methods of anaesthesia interfere little with the integrity of the vasoconstrictor mechanism which is relatively free to exercise the appropriate response to sympathetic stimulation or to circulating pressor substances. Vasopressor responses to reflex stimulation and to the presence of chemical agents, once inhibited or depressed by traditional forms of anaesthesia, are now therefore able to exhibit themselves to the vigilant observer.

Marked elevation of the blood-pressure is undesirable in the normotensive individual under general anaesthesia; still more undesirable is the occurrence of a further rise in the systemic arterial pressure of an already hypertensive patient. The validity of this statement is borne out by the occasional incidence of intracranial vascular catastrophe in this latter combination of circumstances.

Deviations from the normal level of resting blood-pressure are not uncommon in pregnant women, a fact that is not surprising when the numerous and extensive metabolic changes that

accompany this process are taken into account. Hypertension, occurring as part of the clinical picture of pre-eclampsia, not infrequently causes anxiety to the obstetrical anaesthetist. Drugs selected from the anaesthetic pharmacopoeia for administration to toxaemic women must be devoid of vasoconstrictor activity, since the pharmacological activity of vasopressor agents is exaggerated in such subjects (Browne, 1946).

The demonstrable occurrence of an elevation of blood-pressure following intravenous administration of Ergometrine to pre-eclamptic women forms not a small part of the burden of this thesis.

A number of conditions are commonly included in the term "toxaemia of pregnancy" as is evident from the following list, arranged according to the American Committee on Maternal Welfare:-

I. Acute toxaemia of pregnancy.

A. Pre-eclampsia.

1. mild.

2. severe.

B. Eclampsia (convulsions or coma, usually both, when associated with hypertension, proteinuria or oedema).

II. Chronic hypertensive (vascular) disease with pregnancy.

A. Without superimposed acute toxaemia.

1. Hypertension known to have antedated pregnancy

2. Hypertension discovered in pregnancy (before the 24th week and with post-partum persistence).

B. With superimposed acute toxaemia.

III. Unclassified toxaemia (data insufficient to differentiate the diagnosis).

Throughout this thesis, the word "toxaemia" is intended to imply acute toxaemia as defined in group I.

Pre-eclampsia complicates some 6% of pregnancies in the last three months of gestation, and is mostly seen in young primigravidae.

The fact that it is associated with certain maternal and foetal hazards has more than a little bearing on the theme of this investigation.

As far as the mother is concerned, the immediate prognosis depends largely on whether or not eclampsia supervenes, the maternal mortality from pre-eclampsia per se being negligible. The occurrence of eclampsia, however, presents a maternal mortality in the region of 15%.

In New Zealand, eclampsia has been a notifiable disease for over thirty years and, as a result, several interesting surveys have been made (Corkill, 1948, 1954, 1957). Of fourteen fatal cases of eclampsia occurring during the years 1950 - 55 (Corkill, 1957), death was due to massive cerebral haemorrhage (5 cases), sudden cardiac failure (5 cases), and the accidental haemorrhage - anuria syndrome (4 cases). In no case, therefore, was death due to the eclamptic state alone.

Maternal prognosis in terms of morbidity is much more difficult to assess, but

descriptions of varying types of disability, ranging from persistent hypertension to cerebral thrombosis with skeletal paralysis, occupy not a minute part of the obstetrical and general medical literature.

The foetal hazards associated with pre-eclampsia are related largely to the severity of the disease and to the stage in pregnancy at which it first appears. Consideration of the foetal problem, however, is not appropriate to the present study.

In the light of the possible dangers that beset the pre-eclamptic patient, it is obvious that the avoidance of any factor that would tend to aggravate the existing hypertension is of paramount importance. Observation over the past few years of the behaviour of the blood pressure during operative deliveries has shown that, in some women, the intravenous administration of Ergometrine gives rise to a hypertension of sufficient intensity to cause anxiety.

Several factors arising from this observation were in obvious need of examination and prompted the inquiry that has its culmination in this thesis. A hypertensive response appeared to be more frequent in hypertensive than in normotensive patients, yet, despite this general tendency, the appearance of a significant pressor response in some normotensive subjects, and the lack of it in other hypertensive individuals, seemed to merit investigation.

VASOMOTOR TONE IN HEALTH.

The degree of contraction of the smaller blood vessels is controlled by vasomotor nerves belonging to the sympathetic nervous system. These nerves are governed by the continuous activity of the vasomotor centre which is situated in the floor of the fourth ventricle.

Fibres from the vasomotor centre pass down the spinal cord in the white matter of the lateral columns to all the thoracic and the

upper two lumbar segments. There, they form synapses with the connector cells of the sympathetic which lie in the lateral horn of grey matter. The vasomotor nerves issue from the latter to join the sympathetic chains.

The post-ganglionic fibres take origin in the cells of the ganglia of these chains and pass therefrom via the grey rami communicantes to the somatic nerves.

Vasoconstrictor fibres to the blood vessels of the upper limbs are distributed by the mixed nerves of the cervical and brachial plexuses; those controlling the calibre of the arterioles of the lower limbs are carried in the mixed nerves from the lumbar and sacral plexuses.

The function of the vasoconstrictor nerves is to regulate the degree of contraction of the smooth muscle in the walls of the arterioles and veins, and consequently to determine their calibre, an influence that disappears when the nerve supply to the blood vessels is abolished.

This vasoconstriction or tone of central nervous origin is produced by direct and reflex influences on the vasomotor centre. It may be increased in health as part of an emotional response, or as a reaction to sensory stimulation by cold or pain.

The discharge of impulses from the vasomotor centre is also influenced by afferents from the respiratory centre. During the inspiratory phase of respiration, impulses radiate from the respiratory centre, causing an increase in the activity of the vasomotor centre. During the expiratory pause, the influence of the respiratory centre on the latter is diminished.

An adequate carbon dioxide tension is essential to proper functioning of the vasomotor centre. Hyperventilation of the lungs of the experimental animal reduces the carbon dioxide tension in the alveolar air and, therefore, in the arterial blood. Consequently, the vasomotor centre is

inhibited, the discharge of impulses down the vasomotor nerves is decreased, and dilatation of the splanchnic vessels with reduction of blood pressure ensues. Inflation of the lungs with an atmosphere containing an excess of carbon dioxide restores the blood pressure to its previous level. The action of carbon dioxide on the vasomotor centre is twofold; it affects the cells of the centre directly and also reflexly through the chemoreceptors in the carotid and aortic bodies. (Keele & Neil, 1961).

Hyperventilation in man, however, need not be associated with hypotension. This is explained by the fact that hypocarbia exerts a direct vasoconstrictor action on the peripheral blood vessels. The effects of carbon dioxide on the arterioles are, therefore, directly opposite to those produced as a result of its central action.

The initial stimulation of the vasomotor centre that results from hypoxia is due partly to direct action on the vasomotor centre and

partly to reflex stimulation via the chemoreceptors. Unless the hypoxia is relieved, however, the vasomotor centre will fail rapidly.

Of considerable importance is the influence on the activity of the vasomotor centre of the systemic baroreceptors. These lie in the walls of the carotid sinus, aortic arch, pulmonary artery, and all four chambers of the heart. The receptors in the carotid sinus are innervated by branches of the glossopharyngeal, and the others by branches of the vagus nerve. A rise in systemic blood pressure causes stimulation of sino-aortic nerves and, as a result, reflex vasodilatation, a fall in blood pressure, and bradycardia. When the blood pressure falls, the stimulant effect of the nerve endings of the baroreceptors is removed, afferent inhibition of the vasomotor centre is reduced, and the discharge of impulses down the sympathetic vasoconstrictor nerves increased.

In their role of controlling the degree of contraction of the arterioles, vasomotor nerves

are assisted by the presence in the circulation of certain pressor substances, notably the catecholamines, adrenaline and noradrenaline. These nervous and humoral factors act together in the general controlof vascular tone. Local modification of arteriolar contraction may also result from the presence of metabolites, accumulation of carbon dioxide, or changes in the hydrogen ion concentration of the immediate environment.

ABNORMAL INCREASE IN ARTERIOLAR TONE.

Apart from the physiological reflex increase in vasomotor tone that may result from the application of any strong sensory stimulus to the surface of the body, enhanced vascular constriction may result from the pharmacological activity of pressor substances introduced into the blood stream artificially. Pathologically, it may result from the release in abnormal amounts of vasoconstrictor substances, from increased or altered nervous tone, or from a combination of the two.

Increases in vascular tone, unless accompanied by appreciable reduction in cardiac output, result inevitably in elevation of the systemic blood pressure. Such abnormal elevations form a common clinical feature of renal, suprarenal, and intracranial disease.

Two clinical types of hypertension are discernible : (I) primary or essential hypertension, and (2) hypertension secondary to a known pathological condition. Therefore, the two forms of hypertension that will be encountered in the present inquiry, chronic or essential hypertension and hypertensive toxaemia of pregnancy, differ in aetiology as well as in clinical course.

Essential hypertension is characterised in its early stages by an increase in peripheral resistance due to an exaggeration of arteriolar tone. Thus, in its initial phase, the blood pressure of chronic hypertension is subject to considerable fluctuation.

Once established, however, the abnormally

raised arterial pressure becomes stabilised and maintains its height during rest and whilst under sedation. At this stage of development, thickening of the walls and reduction in calibre of the smaller blood vessels is apparent, the left ventricle undergoes hypertrophy, and renal function is impaired.

It follows that, whilst angiospasm is responsible for the increase in peripheral resistance in early chronic hypertension, subsequent alterations in the walls of the arterioles establish that increased resistance as an irreversible feature of the disease. It will be seen from later discussion that this differentiation between early and established chronic hypertension may be of some practical importance in determining the reaction of the patient to the intravenous administration of Ergometrine.

Arteriolar spasm is an essential feature of pre-eclamptic toxaemia of pregnancy (Addis, 1937 ; Mussey, Hunt & Sluder, 1945 ; Whitacre,

Loeb & Chin, 1947). Whether the enhanced arteriolar tone is the basic cause of pre-eclampsia, as claimed by Mengert, Jennett & Brown (1949), or simply a secondary manifestation of the disease, is still open to considerable argument. The facts remain that it exists, that by virtue of the resultant increase in peripheral resistance it produces hypertension, and that it is a menace to the gravid patient in terms of morbidity and mortality, both maternal and foetal.

This thesis purposes to demonstrate the occurrence of a significant hypertensive response when the normally weak and usually ineffectual vasoconstrictor, Ergometrine, is administered to patients with increased arteriolar tone, in particular women suffering from toxaemia of pregnancy.

Some observations on the nature of the angiospasticity of pre-eclampsia are therefore relevant.

ANGIOSPASM IN PRE-ECLAMPSIA.

It is widely accepted that vasospasm is possibly the most important single disorder of physiology in patients suffering from pre-eclampsia. This concept, first elaborated by Volhard (1918), is substantiated by the observations of several investigators, although the debate as to whether it is the primary or a secondary factor of the condition persists.

Evidence of arteriolar spasm is seen in the nail-beds where the resistance results in a degree of circulatory stasis (Hinselmann, 1924). Spasm of the retinal arterioles, too, is a fairly constant feature of pre-eclampsia and eclampsia (Wagener, 1933 ; Hallum, 1936 ; Wagener & Keith, 1939) and in this site, spastic arteriolar contraction can sometimes be seen, in the untreated patient, to proceed to sclerotic changes in the walls of these same vessels.

This latter degenerative change is reputed to be an ischaemic phenomenon and to result from compression of the vasa vasorum

by the continual spasm of the arteriolar wall.

Interference with the blood supply to the kidney causes proteinuria and the occurrence of this urinary abnormality is taken as part evidence that the increase in arteriolar tone, seen throughout the general circulation, affects the kidney also.

In an attempt to elucidate the complexities of the haemodynamic upset in acute toxaemia, several workers have exploited the activity of tetraethylammonium chloride (Garber et al., 1950 ; Assali et al., 1952). The chief function of this compound is to produce blockade of the autonomic ganglia, sympathetic and parasympathetic, so that isolation of the peripheral vascular tree from its neurogenic influences occurs. Under the blocking influence of tetraethylammonium chloride, therefore, the blood pressure is maintained solely by the action of circulating pressor substances on the walls of the blood vessels. When derived of its extrinsic nerve

supply in this manner, the tone of the arterioles decreases and so in normal non-pregnant subjects and in normotensive pregnant women a substantial fall in blood pressure is the rule. The administration of tetraethylammonium chloride to pre-eclamptic patients, however, produces a much smaller depression of the level of blood pressure. This finding is taken as evidence that some humoral mechanism is responsible, at least in part, for the angiospasm and hypertension of pre-eclampsia.

VASOCONSTRICTOR EFFECT OF ERGOMETRINE.

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A. EXPERIMENTAL EVIDENCE.

The year 1935 heralded a new era in the practice of obstetrics. The isolation of a new alkaloid of ergot in that year by four groups of investigators, working independently, altered the prognosis of childbearing for a countless number of women. Dudley and Moir (1935) gave the first detailed description of the method of isolation of the new alkaloid in its crystalline form, together with an account of its physical characteristics and chemical properties. They suggested that their new compound should be called "Ergometrine". Later in the same year, similar publications came from the laboratories of Thompson (1935), Stoll and Burckhardt (1935), and Davis, Adair, Chen and Swanson (1935), relating to compounds named "ergostetrine", "ergobasine", and "ergotocin" respectively. After an exchange of samples of their compounds, it became clear to

the members of all four research teams that ergometrine, ergostetrine, ergobasine and ergotocin were one and the same substance.

Being derived from a fungus whose history in the production of vascular damage and gangrene was notorious, it was obviously desirable to determine whether the action of the new oxytocic principle was to be obtained at the expense of the circulatory hazards associated with the crude preparations of ergot. As a result, the four papers describing the isolation of Ergometrine in its crystalline form, were soon followed by accounts of the vasoconstrictor effects of the substance under experimental conditions.

Two series of optically active, isomeric alkaloids are obtainable from ergot, all derivatives of lysergic acid. The optical isomerism results from the presence in the lysergic acid portion of the molecule of an asymmetric carbon atom. The naturally occurring

alkaloids of ergot, including Ergometrine, are laevorotatory and only such laevorotatory forms are active pharmacologically.

If these naturally-occurring laevorotatory alkaloids are now considered on a basis of pharmacological activity, two distinct groups are discernible. The first group contains alkaloids which depress central vasomotor reflexes and exhibit a powerful blocking action of the pressor effects on sympathetic nerve stimulation. The second group, which includes Ergometrine, consists of alkaloids of lower molecular weight, which have little blocking activity.

Direct stimulation of the smooth muscle of blood vessels, however, is a form of pharmacological activity common to both groups of laevorotatory substances. This property was demonstrated by Brown and Dale (1935) in a study of the effects of intravenous injections of Ergometrine in anaesthetized rabbits and

spinal cat preparations. The hypertension that resulted in both animals was compared with the pressor action of two alkaloids of higher molecular weight, ergotoxine and ergotamine, and it was found that, in the intact rabbit, the vasoconstrictor action of Ergometrine was greater, but in the spinal cat less marked, than the effect of these two compounds.

There followed this study a number of experimental reports whose evidence was, on occasions, conflicting and contradictory, for reasons that include the use of experimental animals of differing species, and the employment of anaesthetics and narcotic agents now known to be powerful ganglionic blockers, or otherwise depressants of the vasoconstrictor mechanism.

Thompson (1937), in a comparison of the pharmacological syndromes of Ergometrine and the ergotoxine group of alkaloids, obtained only a feeble pressor response when Ergometrine was administered intravenously to cats under chlorbutanol narcosis. The same worker obtained

but a slight rise in the blood pressure levels of dogs under thiobarbiturate anaesthesia. In both his series of experiments, therefore, Thompson was employing vasodilator agents as the only form of anaesthesia. Moreover, the thiobarbiturate used in the second group of animals is now known to reduce the adrenergic blocking potency of the ergot alkaloids. In other words, the narcosis under which the animal experiments were conducted, interfered with the action of Ergometrine at a ganglionic level and by direct action on the arteriolar walls. The inference is, therefore, that the pressor response obtained by Thompson was greatly modified.

In vagotomized dogs, under chloralose anaesthesia with intermittent positive-pressure ventilation of the lungs, Ergometrine exerts a powerful pressor effect (Hamet, 1935). A point of particular interest, that may also be of considerable practical significance in patients with pre-eclampsia and women with

concealed accidental haemorrhage, is the finding of this investigator that Ergometrine causes renal vasoconstriction in the vagotomized experimental animal.

Repeated doses of Ergometrine produce a progressively decreasing vasoconstrictor response (Brown & Dale, 1935), a finding characteristic of all the alkaloids of ergot.

The vasoconstrictor action on isolated vessels has also been observed. Ergometrine constricts the leg vessels of the frog (Davis et al., 1935) and the ear vessels of the rabbit (Rothlin, 1935 ; Savini, 1956).

Modification of the vasoconstrictor activity of the ergot alkaloids by some methods of narcosis has been noted already. There follows an account of papers whose evidence seems to conflict with the vasotonic actions already described. All animals, however, were anaesthetized by agents which would interfere greatly with the pharmacological activity of the drug under investigation.

Kothlin (1935) investigated the action of Ergometrine in cats and dogs, and was unable to evoke hypertension in either. This observation, although not appreciated at the time, was due to the fact that the cats were studied under ether, chloralose, and thiobarbiturate anaesthesia, while the dogs were anaesthetized with ether. It was Brown and Dale (1935) who pointed out that anaesthesia, possibly accompanied by respiratory depression and paralysis of the vasomotor centre, accounted for the absence of a pressor response or even the production of a vasodepressor effect. This latter experimental observation has been translated into clinical terms in the current study of the vasopressor effect of Ergometrine in parturient women, and it will be demonstrated later how the systemic effects of Ergometrine may be obviated by employing certain anaesthetic agents.

Despite the fact that Ergometrine has been in clinical use for a period of twenty-five years,

almost all the medical publications relating to its pharmacological activity have dealt with the oxytocic property of the drug. The ability of Ergometrine to control post partum bleeding has won for this agent universal and almost routine adoption in the care of the parturient woman, yet comparatively little study has been devoted to its systemic effects. The presence of any appreciable vasopressor activity in clinical dosage is denied by several standard works (Micks, 1950 ; Smith, 1938 ; Wood - Smith & Stewart, 1962) despite the provision of adequate experimental evidence to suggest its possible existence. At this juncture, a critical evaluation of the few relevant clinical reports is indicated.

B. SYSTEMIC EFFECTS ON PARTURIENT WOMEN.

Dieckmann, Forman and Philips (1950), perturbed by the dogmatic statement in several textbooks of pharmacology that Ergometrine in

therapeutic doses exerts no systemic effects, published a report of the symptomatology of thirty-seven patients who had received 0.4 mg. Ergometrine intravenously. This interesting paper appears to have escaped the notice of a few subsequent writers who still deny that this oxytocic agent can produce side-effects of appreciable severity (Wood-Smith & Stewart, 1962).

The symptoms described by the patients and their respective incidence were as follows:-

abdominal cramp	57%	(due to uterine contraction)
dizziness	19%	
nausea	14%	(vomiting in 1 patient)
headache	14%	

Of twelve women in whom the course of the blood pressure was followed, seven (58%) had a rise in systolic or diastolic level of at least 10 mm.Hg. Unfortunately, no record is given of the resting pressures of the patients in whom a pressor response was evoked.

Schade (1951), in a comparative clinical study of the vasomotor properties of Ergometrine

and Methyl Ergometrine, observed the changes in blood pressure of four hundred parturient women. Half that number received 0.2 mg. Ergometrine and the other half 0.2 mg. Methyl Ergometrine by intravenous injection. A pressure of 140/80 mm.Hg was accepted as upper limit of normal and 20 mm.Hg taken to be a significant elevation. Ten hypertensive patients presented in the series and in six of these, Ergometrine evoked a significant rise in blood pressure.

The results of Schade's investigation and the conclusions drawn from them cannot be accepted without criticism. Firstly, 74% of the women in the Ergometrine series were delivered under spinal analgesia, an effective means of reducing blood pressure, depending on the level reached by the analgesic solution in the subarachnoid space. Neither the type of spinal analgesia nor the level attained is recorded. Secondly, 25.5% of the remaining women in the Ergometrine series were anaesthetized with nitrous oxide, oxygen and

di-ethyl ether, and since it is intended to show later how this very anaesthetic method is an effective means of counteracting the vasopressor activity of Ergometrine, two observations are presented that tend to invalidate the results. One interesting part of this report, however, to which reference will be made later, describes the occurrence of convulsions in the puerperium in a patient delivered of twins and to whom Ergometrine had been administered. In passing, it is to be noted that the intravenous dose of Ergometrine employed in Schade's investigation was less than half the standard intravenous dose used in many obstetric units in Great Britain.

In the following year, Hamilton, Higgins and Alsop, in a comparative study of naturally occurring and synthetic oxytocic agents, reported that in 166 patients who received 0.2 mg. Ergometrine intravenously, a significant hypertensive response (i.e. at least 20 mm.Hg.) was obtained in 12 - 15%. None of the women

in this series had evidence of toxaemia of pregnancy. All were delivered under general anaesthesia, some with nitrous oxide and oxygen, others with nitrous oxide, oxygen and di-ethyl ether. These differences in technique introduce an undesirable variant to the investigation, since pressor responses will be evident under nitrous oxide anaesthesia with adequate oxygenation, but inhibited by ether or by nitrous oxide with sub-oxygenation. Nevertheless, the authors concluded that "elevations in blood pressure resulting from the use of ergonovine (Ergometrine) ..... in the third stage of labour can be effectively reduced by the judicious use of premedication and anaesthesia". A further and interesting observation made by these three investigators was a dramatic hypertensive response occurring in two women who received 0.2 mg. Ergometrine intravenously and 1 cc. 'Pitocin' into the uterine muscle simultaneously.

Another large and more recent study is that

of McGinty (1956). Of two hundred patients in this series who received oxytocic drugs as part of the management of the third stage of labour, fifty were given 0.2 mg. Ergometrine maleate intravenously, and of this latter number, ten out of thirty-eight normotensive and four out of twelve hypertensive patients had a significant rise in systolic blood pressure. As in the series of Schade and of Hamilton and his associates, 20 mm.Hg was considered by McGinty to be an acceptably significant elevation.

It is worthy of note that in McGinty's series all patients had vaginal deliveries under pudendal block analgesia, the latter being achieved with an analgesic solution containing 1 : 100,000 adrenaline. The elevation of systolic blood pressure in the non-toxaemic women was noted to be of a transient nature, in which case the critical observer must assume that the vasopressor agent contained in the analgesic solution had an undesirable generalised

influence on the vascular bed, so tending to invalidate the results of an otherwise well conducted study.

It is evident from consideration of the foregoing reports that there is need for a critical clinical study of the vasopressor activity of Ergometrine in parturient women. It is believed that under modern conditions of anaesthesia, a true index of the vasoconstrictor activity of this drug is obtainable, and to this end the investigation about to be described was instituted.

METHOD OF STUDY.

METHOD OF STUDY.

A. NITROUS OXIDE, OXYGEN, MUSCLE RELAXANT SERIES.

In the first part of this investigation, a study was made of 256 patients requiring general anaesthesia for delivery by obstetric forceps or Caesarean Section, and for the purposes of the inquiry, the anaesthetic technique employed was standard.

Pre-anaesthetic medication consisted of 0.6 mg. atropine sulphate only. Following intravenous induction of anaesthesia with 200 - 250 mg. thiopentone sodium, succinylcholine 60-70 mg. was given to allow immediate endotracheal intubation. Thereafter, intermittent positive-pressure insufflation of the lungs was carried out with nitrous oxide gas and oxygen, succinylcholine being repeated to maintain apnoea and muscular flaccidity. Increments of succinylcholine were of the order of 20 mg., not only because of the danger of cardiac irregularity and standstill with larger amounts, but also because previous experience had shown that

increments in excess of 20 mg. produced spikes of temporary rise in arterial blood pressure.

The dose of Ergometrine maleate was 0.5 mg. in all patients. This was usually administered by intravenous injection at the time of delivery of the anterior shoulder of the baby, but in 21 women, injection of the oxytocic agent was delayed until delivery of the placenta had occurred and uterine contraction and retraction established. This latter group afforded an opportunity to study any alterations in arterial pressure following delivery that might not be attributable to Ergometrine.

In recording the systemic blood pressures the auscultatory method was employed in order to obtain diastolic as well as systolic levels. The basal or resting blood pressure was taken as that pressure recorded on admission, in the case of emergency procedures, or as that found during ante-natal examination, in the case of elective operations. Determination of this basal pressure was made with considerable care

since this reading afforded the only reasonable means of segregating the patients into groups, the pressor values obtained during established labour often bearing little or no relationship to the true resting state of the peripheral vascular bed.

Early in the investigation, it was found that patients exhibiting a vasopressor response did so within two minutes and that after the third minute no further elevation occurred. As a result, only the rise in systemic blood pressure three minutes after administration of Ergometrine is recorded in Tables I - III, although in all patients the readings were charted throughout operation.

All the women studied and whose pressure changes are recorded hereafter were anaesthetized by the author personally. The only cases excluded from the series were patients who required active resuscitation to render them fit for operation and those whose rapid deterioration due to operative haemorrhage rendered them

valueless as far as this study was concerned.

After a study of the series of patients anaesthetized by the thiobarbiturate, muscle relaxant, nitrous oxide and oxygen technique, it was envisaged that by employing vasodilator techniques of anaesthesia, the pressor effect of Ergometrine in toxaemic patients might be modified. Three further anaesthetic sequences were used in selected patients, known to be suffering from established pre-eclamptic toxaemia of pregnancy. These sequences were:-

(1) nitrous oxide, oxygen and halothane in a semi-closed system,

(2) nitrous oxide, oxygen and ether in a semi-closed circuit, and

(3) cyclopropane and oxygen in a closed circuit.

B. HALOTHANE SERIES.

The behaviour under halothane anaesthesia of eight known pre-eclamptic patients was observed. Premedication consisted of atropine

sulphate 0.6 mg. only and was therefore devoid of drugs known to cause vasodepression. Thiopentone sodium 250 mg. was given intravenously to produce unconsciousness, followed by succinylcholine 70 mg. to allow easy and rapid intubation of the trachea. Following isolation of the respiratory tract, the lungs were inflated rhythmically with nitrous oxide and oxygen. Halothane 1.0% was added to the gaseous mixture from a calibrated and temperature-compensated vaporizer. In all eight women the period of respiratory paralysis lasted only a few minutes and all were breathing spontaneously at the time of delivery and of administration of Ergometrine 0.5 mg. intravenously.

The blood pressure readings were recorded by the auscultatory method and at the same times as in the previous series. Deep halothane narcosis was not sought on any occasion and, despite reports that uterine relaxation with this anaesthetic agent may cause abnormal loss of blood (MacKay 1957 ; Russell 1958 ;

Albert et al, 1959 ; Crawford 1962), bleeding was not excessive and the results were not therefore influenced by marked alterations in circulating blood volume.

C. DI-ETHYL ETHER SERIES.

Since the administration of ether anaesthesia is known to cause peripheral vasodilatation, it was next decided to explore the possibility of protecting toxaemic women from the circulatory effects of Ergometrine by administering this anaesthetic agent to a series of six pre-eclamptic patients.

Atropine was given as pre-anaesthetic medication as before, and endotracheal anaesthesia attained by induction with thiopentone sodium and succinylcholine in the dosage employed in the above series. Intermittent positive-pressure insufflation of the lungs was then instituted with nitrous oxide and oxygen, and di-ethyl ether vapour added to the mixture during the period of apnoea. The gases and vapour were

delivered to the patients via a Magill semi-closed apparatus. Once spontaneous respiration had been re-established, a plane of moderate surgical anaesthesia was sought before delivery of the baby occurred. Thus all six women were breathing spontaneously and were at a comparable level of anaesthesia when 0.5 mg. Ergometrine was administered intravenously.

Alterations in blood pressure were noted and in particular changes three minutes after injection of the oxytocic agent.

Patient number 6 in this series (see Table X), the most severely hypertensive of the group, had an eclamptic convulsion immediately prior to induction of anaesthesia.

D. CYCLOPROPANE SERIES.

The vasodilator effect of cyclopropane and its influence on the Ergometrine effect were investigated in two ways; firstly to a group of five pre-eclamptic women cyclopropane

and oxygen were given as the sole agents from a Boyle mark II closed circuit apparatus in order to determine what degree of protection might be afforded against the vasoconstrictor activity of Ergometrine, and secondly, in two pre-eclamptic women in whom Ergometrine had evoked a pressor response, the effect of cyclopropane was observed.

The provision of anaesthesia for assisted breech delivery presents a problem that is peculiar to this obstetric manoeuvre. In this type of delivery, the voluntary efforts of the patient are employed to effect delivery of the breech as far as the scapulae. The head is then delivered with the mother anaesthetized so that moulding and re-expansion of the foetal head might be controlled and the danger of intracranial haemorrhage be eliminated or reduced. Such a mode of delivery calls for induction of anaesthesia with the patient in the lithotomy position, in violation of the laws of obstetric anaesthesia.

From the point of view of the present inquiry, inhalation of cyclopropane and oxygen provides a convenient method of anaesthesia since this hydrocarbon produces a relatively pleasant and rapid induction of unconsciousness, light anaesthesia for delivery of the foetal head with considerable maternal safety and marked dilatation of the peripheral vascular bed.

The vasodilator effect of cyclopropane is maximal under light anaesthesia (Kitchen et al., 1953) ; thus in all five toxaemic patients anaesthetized in this manner for assisted breech delivery, a considerable degree of vasodilator activity was present when Ergometrine 0.5 mg. was given intravenously.

During anaesthesia with nitrous oxide, oxygen and succinylcholine, two patients suffering from pre-eclampsia produced an elevation of blood pressure after intravenous Ergometrine. Cyclopropane was added to the gaseous mixture and the alterations in pressure recorded.

E. PETHIDINE SERIES.

It is common practice to enhance per-operative maternal analgesia by administration of intravenous pethidine, but since this drug is a profound depressant of the respiratory centres, it is proper policy to withhold it until delivery of the baby has been executed.

As pethidine is reputed to have a papaverine-like effect on the smooth muscle of the smaller blood vessels (Gunn, 1948), it seemed logical to determine whether or not its administration was effective in modifying the rise in blood pressure produced by Ergometrine.

Pethidine hydrochloride 50 mg. was given by intravenous injection to thirteen women in whom a pressor response had been evoked by the ergot alkaloid and the systemic blood pressure observed carefully.

R E S U L T S.

RESULTS.

A. NITROUS OXIDE, OXYGEN, RELAXANT SERIES.

On account of the large number of patients investigated in this series, the detailed readings of blood pressure, from which Tables I, II, and III are compiled, are to be found in Appendices A, B, and C respectively.

In the 256 patients to whom Ergometrine was administered, the arterial blood pressure was recorded at three specific stages in the procedure : (I) preoperatively or on admission, (2) at the moment of intravenous injection of the drug, and (3) three minutes after the injection.

For the purpose of analysis of the results, the cases were arranged in ascending order of basal diastolic pressure.

From a statistical viewpoint, classification of the cases studied is important and the establishment of a group of normotensive individuals necessary. Opinion as to the

TABLE I.

PRESSOR RESPONSE TO INTRAVENOUS ERGOMETRINE IN 169 PATIENTS WITH BASAL DIASTOLIC BLOOD PRESSURE OF LESS THAN 90 mm.Hg.

Basal diastolic blood pressure mm.	Total number of patients.	Number of patients showing rise in systolic pressure of						
		0 - 4 mm	5 - 9 mm	10-14 mm	15-19 mm	20-24 mm	25-29 mm	⩾30mm
60 - 64	2.	2.	-	-	-	-	-	-
65 - 69	9.	6.	1.	1.	1.	-	-	-
70 - 74	56.	49.	4.	3.	-	-	-	-
75 - 79	20.	13.	1.	2.	1.	-	1.	2.
80 - 84	75.	51.	7.	11.	1.	2.	2.	1.
85 - 89	7.	7.	-	-	-	-	-	-
	169.	128.	13.	17.	3.	2.	3.	3.

acceptable upper limit of normal blood pressure in pregnancy varies and different authors have set their own standards of normality. Browne (1946) considered that any reading greater than 120/80 mm.Hg., should be regarded as abnormal, whereas de Lee and Greenhill (1948) and McIlroy (1936) define abnormal arterial pressure in pregnancy as being one greater than 130/90 mm.Hg. For the purpose of this investigation, the author has accepted a diastolic blood pressure of less than 90 mm.Hg., as being normal. Table I and Appendix A contain the details of patients of this supposedly normotensive group. The remaining women were placed in two further groups, depending on whether the resting diastolic pressure was between 90 and 99 mm.Hg., or greater than 100 mm.Hg. Details of the second group are contained in Table II and Appendix B, and of the third in Table III and Appendix C.

169 women presented in the normotensive category (Table I). Of these, eight showed

TABLE II.

PRESSOR RESPONSE TO INTRAVENOUS ERGOMETRINE IN 53 PATIENTS WITH BASAL DIASTOLIC BLOOD PRESSURES OF 90 - 99 mm.Hg.

Basal DBP, mm.Hg	No. of patients	Number of patients showing rise in systolic pressure of									
		0-4mm	5-9mm	10-14mm	15-19mm	20-24mm	25-29mm	30-34mm	35-39mm	40-44mm	⩾45mm
90 - 94	39.	13.	3.	11.	9.	2.	1.	-.	-.	-.	-.
95 - 99	14.	5.	0.	3.	2.	1.	-.	2.	-.	-.	1.
	53.	18.	3.	14.	11.	3.	1.	2.	0.	0.	1.

an elevation of blood pressure of at least 20 mm.Hg., following the intravenous injection of Ergometrine. Seven twin pregnancies occurred in this group and one is compelled to draw attention to the fact that of the eight normotensive patients who showed a significant response (4.7%), plural pregnancy accounted for five. One other of the eight had oedema and albuminuria, despite a basal systemic pressure of 120/80 mm.Hg.

The second category (Table II) is composed of the 53 patients with basal preoperative diastolic pressures of between 90 and 99 mm.Hg., and might be considered to be a mixed group of normotensive and pre-eclamptic individuals.

Within this range of diastolic blood pressure there was a marked increase in the percentage of cases showing an elevation of 20 mm.Hg., seven women (13.2%) exhibiting a response of that order.

Of women in the second group who failed to show a marked elevation, two suffered from

TABLE III.

PRESSOR RESPONSE TO INTRAVENOUS ERGOMETRINE IN 31 PATIENTS WITH DIASTOLIC BLOOD PRESSURE OF 100 mm.Hg OR MORE.

Basal DBP mm.Hg.	No. of patients.	Number of patients showing rise in systolic pressure of								
		0-4mm	5-9mm	10-14mm	15-19mm	20-24mm	25-29mm	30-34mm	35-39mm	40-44mm
100 - 104	14.	1	-	3	1	4	0	1	1	3
105 - 109	5.	1	2	1	-	-	-	-	1	-
110 - 114	7.	2	-	-	-	2	1	-	-	2
115 - 119	2.	2	-	-	-	-	-	-	-	-
⩾ 120	3.	2	1	-	-	-	-	-	-	-
	31.	8.	3	4	1	6	1	1	2	5

diabetes, two had renal disease, and three carried a preoperative diagnosis of chronic hypertension. As one might expect, the patients with essential hypertension were of the higher age group, two being thirty-eight and one forty years of age. Two patients, both with clinical features of severe toxaemia of pregnancy, sustained a significant fall in blood pressure after injection of the ergot alkaloid.

Cases with a diastolic blood pressure of at least 100 mm.Hg., are detailed in Table III and number thirty-one of the total. Intravenous injection of Ergometrine evoked an elevation of blood pressure of at least 20 mm.Hg., in fifteen members of this group (48.4%).

Of the women who retained their pre-ergometrine level of systemic pressure, one, who had had an eclamptic seizure and who subsequently gave birth to twins, was under moderately deep tribromethanol narcosis at the time of induction of surgical anaesthesia. Intravenous injection of the alkaloid caused no

rise in her arterial blood pressure.

The blood pressure fell in one severely toxaemic patient from 170/120 mm.Hg., to 150/106 mm.Hg., and this drop coincided with delivery and injection of the oxytocic agent. It is worthy of note that only eleven patients within this range of basal blood pressure showed a response of less than 10 mm.Hg. Eight of these suffered from chronic hypertensive cardiovascular disease and were, moreover, the oldest women in the group, one being aged 36, two aged 37, two aged 39, one 42 and another 44 years.

The last five patients of the series, all with a resting diastolic pressure of more than 110 mm.Hg., showed no appreciable alteration in the pre-ergometrine level despite the obvious general increase in incidence of pressor response with height of basal pressure. Thus there is a tendency for the vasoconstrictor response to Ergometrine to increase with height of resting blood pressure up to the region of 110 mm.Hg.,

TABLE IV.

VASOPRESSOR EFFECT OF ERGOMETRINE - INCIDENCE OF SIGNIFICANT ELEVATION COMPARED WITH LEVEL OF RESTING DIASTOLIC BLOOD PRESSURE.

	Basal diastolic blood pressure of			
	90 mm.Hg.	90 - 99 mm.Hg	100 - 109 mm.Hg	⩾110 mm.Hg.
Number of patients	169.	53.	19.	12.
Rise of ⩾ 20 mm.Hg in	4.7%	13.2%	52.6%	41.7%

diastolic ; thereafter, the frequency of response in this series of patients decreases. This feature is evident from reference to Table IV.

STATISTICAL ANALYSIS.

The decrease in frequency of the vasopressor response in patients with a diastolic pressure of more than 110 mm.Hg., results from the fact that none of the patients with established chronic hypertensive cardiovascular disease exhibited any appreciable alteration in pressure after delivery. It is obvious, therefore, on clinical grounds alone, that this group interferes with the general trend of increasing incidence of vasoconstrictor response with ascending height of basal blood pressure, so that before the three groups of patients in Tables I, II, and III will bear statistical comparison, all cases of chronic hypertension must be excluded from the entire series.

Furthermore, it has been noted that the

TABLE V.

COMPARISON OF PRESSOR RESPONSE IN THREE GROUPS OF WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

(Patients with twin pregnancy & chronic hypertension excluded)

Rise in Systolic BP mm.Hg.	Number of Patients.				
	DBP < 90 mm.	DBP 90 - 99 mm.	DBP ⩾ 100 mm.		
0 - 19	159 (98.1%)	42 (87.5%)	6 (28.6%)	207	
⩾ 20	3 (1.9%)	6 (12.5%)	15 (71.4%)	24	
	162	48	21	231	

incidence of elevation of blood pressure after intravenous injection of Ergometrine is much higher in normotensive twin pregnancy than in the single pregnancies occurring in the normotensive category. All cases of twin pregnancy are therefore excluded also from the corrected Table V.

It has been suspected clinically from the results of Tables I - III that in the absence of chronic hypertension, the greater the basal diastolic blood pressure, the more likely will Ergometrine evoke a vasoconstrictor response. Also, it appears that the greater the resting pressure, the more severe the individual elevation. In short, the vasopressor response to intravenous Ergometrine increases in incidence and degree with basal diastolic blood pressure.

That this clinical suspicion is not without reason has been borne out by analysis of the corrected figures for the series (Table V). By employing the X^2 test it was shown that the difference in frequency of marked pressor

activity (i.e. a rise in systolic pressure of at least 20 mm.Hg.) between patients of Table I and Table II is significant and between patients of Table II and Table III more so, all women with chronic hypertension or twin pregnancy excluded. The actual values obtained for X^2 were 7.8 ($P<0.01$) and 21.3 ($P<0.001$) respectively.

PRESSOR EFFECT OF ERGOMETRINE IN TWIN PREGNANCY.

Ten twin pregnancies occurred in the course of the investigation. Five of seven falling into the normotensive category showed a significant elevation of blood pressure, one a rise of 12/6 mm.Hg., and the seventh no alteration from the pre-ergometrine level. Of the three hypertensive mothers, a significant response was elicited in one, a rise of 14/10 mm.Hg., in the second, and no response in the third who was under the narcotic influence of tribromethanol.

Thus the incidence of appreciable vasoconstriction following Ergometrine in

TABLE VI.

RESPONSE IN NORMOTENSIVE TWIN PREGNANCY COMPARED WITH THAT IN NORMOTENSIVE SINGLE PREGNANCY.

Rise in BP, mm.Hg.	Number of Twin Pregnancies	Number of Single Pregnancies
0 - 19	2 (28.6%)	159 (98.1%)
20 -	5 (71.4%)	3 (28.6%)
TOTALS	7.	162.

uncomplicated twin pregnancy is much higher than in other normotensive women, as is shown in Table VI. The statistical significance of this variation of response in normotensive women was calculated from Table VI thus:-

$$X^2 = \frac{(159x5 - 2x3 - \frac{169}{2})^2 \, 169}{161x8x162x9}$$

$$= \frac{83,878,122.25}{1,460,592}$$

$$= 57.9 \quad (P<0.05)$$

The X^2 test, therefore, shows that there is a significant difference between normotensive twin pregnancy and normotensive single pregnancy with respect to incidence of Ergometrine effect.

PRESSOR EFFECT OF ERGOMETRINE IN CHRONIC HYPERTENSIVE CARDIOVASCULAR DISEASE.

Essential hypertension was diagnosed preoperatively in twelve women treated in the course of this inquiry. Despite the high resting diastolic blood pressures of these patients, none shared in the general tendency of hypertensive women to exhibit a significant elevation in

TABLE VII.

RESPONSE TO INTRAVENOUS ERGOMETRINE IN PATIENTS WITH CHRONIC HYPERTENSION.

Rise in Systolic BP, mm.Hg.	Basal diastolic blood pressure, mm.Hg.	
	90 - 99	⩾ 100
0.	2.	2.
1 - 9.	1.	5.
10 - 19.	1.	1.
⩾ 20.	0.	0.
	4.	8.

pressure following injection of Ergometrine (Table VII). This difference in response in the two hypertensive groups, toxaemic and chronic, is significant.

Apart from patients who presented with a well-defined picture of chronic hypertension, there existed in the series, without doubt, patients with minor degrees of hypertensive cardiovascular disease, perhaps co-existing with hypertensive toxaemia.

INFLUENCE OF UTERINE CONTRACTION AND RETRACTION ON MATERNAL BLOOD PRESSURE.

It is a popular belief that uterine contraction and retraction occurring after delivery of the placenta increase the circulating blood volume to such a degree that a rise in systemic blood pressure might be expected. Two features of the current study contest this argument strongly. Firstly, a great many patients in the normotensive category showed no difference between their pre - and post -

TABLE VIII.

RECORD OF BLOOD PRESSURE IN 21 PATIENTS TO SHOW

(a) pressure changes following delivery when Ergometrine is withheld,

(b) any subsequent alteration due to pressor activity of Ergometrine.

Basal BP mm.Hg.	BP at delivery mm.Hg.	BP at time of I.V. Injection mm.Hg.	Alteration in BP. mm.Hg.	Delivery-Injection Interval mins.	Rise in BP after I.V. Ergometrine mm.Hg.
100/65	140/100	140/100	0/0	3.	0/0
100/65	150/104	146/104	-4/0	7.	0/0
115/70	142/98	142/98	0/0	5.	0/0
120/70	146/86	140/84	-6/-2	6.	0/4
120/80	150/104	146/104	-4/0	3.	6/4
120/80	140/96	140/96	0/0	6.	0/0
120/84	164/120	164/120	0/0	3.	0/0
120/84	144/108	142/108	-2/0	3.	4/8
120/85	132/94	134/94	+2/0	3.	4/4
122/92	108/84	112/86	+4/+2	5.	6/0
124/96	144/90	144/92	0/+2	3.	0/2
126/90	126/90	130/90	+4/0	3.	10/8
130/80	120/76	120/80	0/+4	3	10/4
130/85	140/92	140/94	0/+2	5.	10/4
130/90	120/86	120/88	0/+2	3.	0/2
140/90	132/90	130/90	-2/0	3.	10/10
140/96	164/108	164/110	0/+2	6.	16/6
140/100	148/96	148/98	0/+2	5.	18/10
140/100	140/100	140/100	0/0	3.	30/22
144/116	184/132	186/134	+2/+2	3.	0/0
156/90	140/84	142/84	+2/0	6.	10/4

Ergometrine levels of blood pressure. Secondly, to exclude this contention completely, the administration of Ergometrine to twenty-one women was delayed for some time after delivery of the placenta and the demonstration of good uterine retraction. Any alterations in pressure occurring in the period between delivery of the baby and subsequent administration of Ergometrine were recorded and are presented in Table VIII. It is clear from the results of this delayed injection that uterine contraction and retraction alter the systemic blood pressure little, if at all. The only alterations in pressure are obviously due to the pressor activity of the ergot alkaloid.

DURATION OF PRESSOR RESPONSE TO ERGOMETRINE.

The duration of the circulatory response to Ergometrine is one of obvious practical importance. In women delivered by forceps, no definite conclusion could be reached in this respect since the procedure terminated in all cases while the

pressor effect was still maximal. Thereafter, the influence of narcotic medication, the amount of handling, environmental and bed temperatures, and return of voluntary activity combined to produce an undecipherable and statistically valueless picture.

Greater opportunity for observation of this aspect of the study was afforded by the cases of Caesarean Section. The average duration of this operation, from intubation to withdrawal of anaesthesia, is in the region of 45 minutes, and no noticeable decline occurs until the operation is drawing to a close, i.e. about thirty minutes after the actual delivery. Nine cases of Caesarean Section, however, during which an appreciable rise in blood pressure had occurred, lasted over ninety minutes and in each the blood pressure had returned to the pre-ergometrine level by the end of the procedure. From this observation it is concluded that the duration of the ergometrine effect is in the region of one hour, the maximal response remaining in

evidence for thirty minutes.

B. HALOTHANE SERIES.

In the subsequent series, we shall consider patients in whom a preoperative diagnosis of pre-eclamptic toxaemia had been established. The results obtained in these toxaemic patients under alternative forms of anaesthesia should be examined in the light of the findings of the nitrous oxide, oxygen, relaxant series as a control. The lack of interference with the integrity of the vasoconstrictor mechanism by the gas, oxygen succinylcholine technique is to be stressed in this respect ; this anaesthetic sequence probably gives an even better control than conscious subjects, in whom such factors as exaggerated psychomotor activity and voluntary movement associated with spontaneous vaginal delivery might give a less true index of the behaviour of the systemic blood pressure after administration of Ergometrine.

The readings obtained from the eight patients

TABLE IX.

PRESSOR EFFECT OF ERGOMETRINE.

CHANGES IN BLOOD PRESSURE DURING HALOTHANE ANAESTHESIA.

Identification Number	Age	Basal BP mm.Hg.	BP at time of I.V. Ergometrine	Rise after 3 mins. mm.Hg.
1.	28.	140/90	154/114	0/0
2.	28.	150/90	132/94	0/0
3.	30.	160/90	140/94	4/0
4.	28.	130/94	136/90	4/0
5.	27.	160/98	140/94	0/0
6.	24.	140/100	140/96	4/0
7.	46.	160/108	126/88	12/10
8.	31.	180/130	160/122	12/8

anaesthetized with nitrous oxide, oxygen, and halothane are recorded in Table IX in order of ascending basal diastolic blood pressure. In this Table, both the hypertensive groups examined in the previous series are represented.

Ergometrine 0.5 mg. produced a recognisable elevation of blood pressure in two severely pre-eclamptic women whose respective basal pressures were 160/108 mm.Hg., and 180/130 mm.Hg. In each the rise was of the order of 12 mm. If, as in the previous series, 20 mm., is considered as a significant rise, then in no patient under halothane anaesthesia did Ergometrine evoke a significant pressor response. This result contrasts markedly with the results recorded in Table IV.

It is concluded from the foregoing results that halothane anaesthesia inhibits the pressor response to intravenous Ergometrine in pre-eclamptic women. The statistical significance of the results will be considered later.

TABLE X.

PRESSOR EFFECT OF ERGOMETRINE.

CHANGES IN BLOOD PRESSURE DURING DI-ETHYL ETHER ANAESTHESIA.

Identification number.	Age	Basal BP mm.Hg.	Bp at time of I.V. Ergometrine mm.Hg.	Rise after 3 mins. mm.Hg.
1.	30.	134/92	124/90	0/0
2.	22.	130/96	134/98	0/0
3.	35.	140/96	124/90	0/0
4.	17.	146/96	150/96	6/0
5.	19.	132/104	126/90	0/0
6.	21.	170/110	164/106	2/4

C. DI-ETHYL ETHER SERIES.

Di-ethyl ether was employed to provide surgical anaesthesia for six cases of delivery by obstetric forceps. The two hypertensive groups established in the control series will be found to be represented in the records of blood pressure Table X. None of the four moderately or two severely toxaemic women experienced an appreciable alteration in systolic pressure. In this group of pre-eclamptic patients, therefore, ether appeared to afford complete protection from the vasoconstrictor activity of Ergometrine.

D. CYCLOPROPANE SERIES.

Part (I) of Table XI records the blood pressure readings obtained in the series of breech deliveries under cyclopropane : oxygen anaesthesia. The intravenous injection of Ergometrine caused no alteration in the systemic blood pressure of four of the five subjects studied. The elevation in the fourth was of

TABLE XI.

PRESSOR EFFECT OF ERGOMETRINE.

CHANGES IN BLOOD PRESSURE DURING CYCLOPROPANE ANAESTHESIA.

(1) Induction and maintenance of anaesthesia with cyclopropane.

Identification Number,	Age.	Basal BP mm.Hg.	BP at time of I.V. Ergometrine mm.Hg.	Rise after 3 mins.
1.	33.	134/90	144/96	6/4
2.	34.	136/94	130/100	0/0
3.	23.	136/96	126/90	0/0
4.	20.	140/96	126/90	0/0
5.	24.	154/100	140/94	0/0

(2) Induction with thiopentone, succinylcholine, followed by nitrous oxide and oxygen. Cyclopropane after establishment of pressor response.

Identification Number.	Age.	Basal BP mm.Hg.	BP at time of I.V.Ergometrine. mm.Hg.	Rise after 3 mins. mm.Hg.	BP after 10 mins. of cyclopropane
1.	23.	140/90	126/96	28/4	120/94
2.	31.	140/100	140/100	40/24	150/104

no significance.

It is shown by Part(2) of the same Table that light cyclopropane anaesthesia will, moreover, abolish an already established vasopressor response produced by the same oxytocic drug.

STATISTICAL ANALYSIS OF GROUPS B, C, AND D.

The group of women in Table II, whose basal diastolic blood pressure was between 90 and 99 mm.Hg., is a heterogeneous one, there being contained therein normotensive individuals, chronic hypertensives, and pre-eclamptic patients. Thus it would require an exceedingly large number of cases under alternative forms of anaesthesia in order to establish a significant difference in response to Ergometrine.

On the other hand, few cases are required to establish any difference between groups of patients whose basal diastolic blood pressure is 100 mm.Hg. The patients in the control series with hypertension of this order were compared with the six grossly hypertensive

TABLE XII.

RESPONSE TO ERGOMETRINE IN HYPERTENSIVE WOMEN - INFLUENCE OF ANAESTHETIC TECHNIQUE.

(Patients with chronic hypertension and twin pregnancy excluded)

	Gas : oxygen : relaxant.	Gas : oxygen : halothane.	Gas : oxygen : ether.	Cyclopropane : oxygen.
No. of patients	71.	8.	6.	5.
Incidence of rise of $\geqslant$ 20 mm.Hg.	31.0%.	0%.	0%.	0%.

TABLE XIII.

PRESSOR EFFECT OF ERGOMETRINE.

INFLUENCE OF PETHIDINE HYDROCHLORIDE 50 mg. INTRAVENOUSLY.

Rise in systolic BP following Ergometrine, mm.Hg.	Number of Patients	Average drop in BP after Pethidine, mm.Hg.
10 - 19.	10	3.8
20.	3	2.7

subjects anaesthetized by vasodilator techniques. The value obtained for X^2 was 6.97 ($P<0.01$), thus establishing a significant difference in response to intravenous Ergometrine.

E. PETHIDINE SERIES.

The effect of intravenous pethidine on the circulatory response to Ergometrine is negligible, as will be seen from reference to Table XIII across. In the two groups studied, the average drop in pressure after receiving pethidine was 3.8 mm.Hg., in the one and 2.7 mm.Hg., in the other. This result indicates that any papaverine - like action attributable to pethidine is very weak and certainly of no value in the protection of susceptible subjects from the vasoconstrictor activity of Ergometrine.

D I S C U S S I O N.

DISCUSSION.

A. THEORETICAL CONSIDERATIONS.

The alkaloids of ergot may be divided into two groups on a basis of pharmacological activity. The first group contains the alkaloids of higher molecular weight. These are noted for the complex effects on the cardiovascular system that result from their ability to depress central vasomotor reflexes and to block the pressor effects of sympathetic nerve stimulation. The second group, of which Ergometrine is a member, shows little adrenergic blocking activity.

One form of activity common to both groups is direct stimulation of the smooth musculature of blood vessels with consequent vasoconstriction. This effect has been demonstrated experimentally by perfusion of isolated blood vessels and by administration of the compounds to pithed and intact experimental animals.

This direct and non-adrenergic form of vascular activity is pronounced in the ergot

alkaloids of higher molecular weight, such as ergometrine, ergosine and ergocristine. Moreover, these same compounds produce capillary endothelial damage, vascular thrombosis, and tissue gangrene.

Of all the naturally occurring alkaloids of ergot, Ergometrine probably possesses the least vasoconstrictor activity. Gangrene has never been attributed to the administration of Ergometrine, and vasoconstrictor activity is believed to parallel the tendency of these substances to precipitate gangrene (Goodman & Gilman, 1960).

Relatively little study has been devoted to the vasopressor effects of Ergometrine; indeed some standard works attribute no such activity to it within the therapeutic range (Wood - Smith and Stewart, 1962 ; Douthwaite, 1949 ; Micks, 1950). Nevertheless, there does exist experimental evidence in support of the pressor action of this alkaloid, and clinical experience has resulted in the occasional report in medical literature

of hypertension following exhibition of the drug in obstetrics, (Forman & Sullivan, 1952 ; Dieckmann et al., 1950 ; Schade, 1951 ; Hamilton et al., 1952 ; McGinty, 1956).

PRESSOR RESPONSE IN PRE-ECLAMPSIA.

The results obtained in this investigation from the 256 patients anaesthetized by the thiopentone, succinylcholine, nitrous oxide, oxygen sequence, demonstrates an interesting relationship between the vasopressor action of Ergometrine maleate and differing states of cardiovascular integrity - normotension, hypertensive toxaemia of pregnancy, and chronic hypertension complicating pregnancy.

The most compelling feature portrayed by Tables I - IV is the fact that a high percentage of women with pre-eclamptic toxaemia of pregnancy respond to the intravenous injection of 0.5 mg. Ergometrine by producing a significant elevation in systemic blood pressure. That there is in pre-eclampsia an abnormal sensitivity of the

vasoconstrictor mechanism was first shown by Shockaert and Lambillon (1937) who discovered that normal gravid women and women suffering from pre-eclamptic toxaemia react differently to injections of 'Tonephin', the toxaemic patients being much more responsive. Simultaneously, Dieckmann and Michel (1937) obtained similar results from the administration of pituitrin to nulliparous women, healthy pregnant women, and patients with hypertensive toxaemia. Confirmation of the results of these two studies followed from de Valera and Kellar (1938) and Mukherjee (1941), also using pituitrin, and from Dieckmann (1941), employing on this occasion the cold pressor test.

The results of the investigations of all these authors agree that in patients suffering from acute toxaemia of pregnancy, as compared with the nulliparous female, and the healthy gravida at term, a marked pressor response will be elicited by a standard amount of pressor agent. Browne (1946) had the opportunity of

noting the difference in pressor response to 'Tonephin' 0.66 cc. intravenously in two patients who subsequently developed pre-eclamptic toxaemia, and found that, after developing toxaemia, these women, previously normal, had an abnormal increase in sensitivity of the vascular bed. In one patient the pressor agent caused a rise in systolic blood pressure from 100 mm to 170 mm.Hg., and in the other from 132 mm to 190 mm.Hg.

It appears from Table I that the well-integrated vasomotor mechanism of the healthy, normotensive parturient woman is relatively unresponsive to the pressor activity of Ergometrine. On the other hand, Tables II and III bear ample evidence that the vascular bed of the toxaemic patient reacts to Ergometrine, administered intravenously, by constriction. This finding is in keeping with the observations of the authors quoted above in respect of other vasopressor agents.

Since Ergometrine in the dosage employed is alone incapable of evoking a pressor response

in the normotensive individual, it is possible that abnormal sensitivity of the vascular bed is not the sole reason for the increase in systemic blood pressure in toxaemic women. It may be that Ergometrine and a pressor substance responsible for the already existing hypertension of pre-eclampsia react synergistically. Weight is given to this suggestion by the fact that marked hypertension can be produced in previously normotensive individuals by Ergometrine in combination with certain other pressor agents.

Casady, Moore and Bridenbaugh (1960) examined the obstetric records of 737 women who had had vaginal deliveries under caudal extradural analgesia. In order to counteract any drop in blood pressure, 8 - 12 mg., methoxamine had been given as a routine measure on completion of the block. At the time of placental delivery, Ergometrine 0.23 mg. or methyl ergometrine 0.2 mg. was given intravenously. Severe hypertension from the combined effect of the peripheral vasoconstrictor and the oxytocic agent resulted

in 34 patients, one of whom developed a subarachnoid haemorrhage when an intracranial aneurysm ruptured at a blood pressure of 180/120 mm.Hg.

Oxytocin contains the oxytocic principle of the posterior pituitary gland, and whilst relatively free from vasopressin, it is not completely so (Dundee, 1958). In consideration of the fact that the existence of a state of abnormal sensitivity of the vasoconstrictor mechanism, whether due to a circulating pressor agent in pre-eclampsia, or to an artificially introduced vasopressor drug such as methoxamine, enhances the likelihood of a hypertensive response to Ergometrine, it is not surprising that there should appear in the literature accounts of dramatic elevations of blood pressure in women who have received a combination of Ergometrine and oxytocin. Hamilton et al., (1952) cite two instances in which the simultaneous injection of Ergometrine 0.2 mg., into a vein and of 'Pitocin' 1 cc. into the myometrium

precipitated such a hypertension in previously normotensive women. The blood pressure rose from 118/72 mm. to 178/100 mm.Hg., in one and from 112/68 mm. to 180/110 mm.Hg., in the other.

Of three women in the current inquiry who received 0.5 mg. Ergometrine intravenously while, or just after, having an infusion of synthetic oxytocin ('Syntocinon'), none displayed an appreciable rise in pressure. Without doubt, this contrast in side-effect between the naturally-occurring and synthetically produced compounds, stems from the absence of any vasopressor element in the latter.

When the sympathetic system is blocked during anaesthesia, most of the normal compensatory vascular mechanisms are abolished and a great augmentation of response to vasoactive drugs occurs (Bromage, 1954). It is possible, therefore, to postulate an alternative explanation for the severe hypertension that may follow the combined use of Ergometrine and other vasopressor agents. Substances which block autonomic

ganglionic transmission increase the response of the arteriolar system to a variety of circulating pressor agents. This effect has been demonstrated on cats, dogs, rats and human beings by Page and Taylor (1950).

The mechanism of augmentation was shown by these workers to be due chiefly to loss of inhibitory or compensatory nervous mechanisms, which, in the intact individual, tend to oppose changes in blood pressure. However, any effect on the autonomic ganglia exerted by Ergometrine is not to be compared in potency with the blocking effect of the alkaloids of ergot that possess a polypeptide side-chain.

SYSTEMIC EFFECT OF ERGOMETRINE IN CHRONIC HYPERTENSIVES.

Table IV affords evidence that in the severely hypertensive group, i.e. women with a resting diastolic blood pressure greater than 110 mm.Hg., the incidence of the vasoconstrictor response is decreased. This apparent discrepancy

results from the fact that many of the obstetric patients encountered with a systemic pressure of this order, suffer from a chronic form of hypertensive cardiovascular disease, and not from hypertensive toxaemia of pregnancy. The exclusion of the chronic hypertensives from Table III produces a vastly different incidence of pressor response to the ergot alkaloid, (Table V).

Eleven of the patients anaesthetized by the barbiturate, muscle relaxant, nitrous oxide gas and oxygen technique bore an ante-natal diagnosis of chronic hypertension. All but one failed to show an elevation in systemic blood pressure after intravenous injection of the oxytocic agent. The exception, whose basal pressure was 160/100 mm.Hg., produced an elevation of 12/6 mm.Hg., three minutes after injection, modest indeed in comparison with the elevations elicited in other women of comparable resting blood pressure. Obviously, then, women who suffer from severe chronic hypertension and

who are free from the clinical features of toxaemia, do not exhibit a vasoconstrictor response to Ergometrine administered intravenously.

One patient in the series suffered from hypertension of chronic nephritis and presented with a resting blood pressure of 145/95 mm.Hg. Her pre-ergometrine level of pressure was maintained following injection of the alkaloid.

The above findings in respect of patients with chronic hypertension can be associated with the fact that the systemic blood pressures of pre-eclamptic patients and of women with hypertensive cardiovascular disease differ in spontaneous behaviour. Wërko and Brody (1953) found that the blood pressure in hypertensive cardiovascular disease did not share the spontaneous diurnal variability of the blood pressure in pre-eclamptic toxaemia.

Hammarström, six years previously, had shown that the absence of variability of the blood pressure in hypertensive cardiovascular

disease was also characteristic of chronic nephritis.

It is possible that Table II contains some cases of early essential hypertension, and also possible that any such patients might produce a response to intravenous Ergometrine of the type seen in pre-eclamptic women. Before structural changes become established in the arteriolar wall of the early chronic hypertensive individual, the mechanism responsible for the increase in peripheral resistance is an active contraction of the vessel, due to sympathetic hyperactivity, or to the influence of some circulating vasopressor agent, or perhaps to a combination of the two. It is known that in this early phase, patients show considerable fluctuations of systolic blood pressure with exaggerated responses to application of sensory stimuli or to emotional stress. It is not, therefore, beyond the realms of possibility that the lack of response to Ergometrine in chronic hypertension applies only to patients in whose arterioles

histological changes have already occurred and whose range of pressure change has, for this latter reason, become limited.

ASSOCIATION OF THE PRESSOR EFFECT WITH PLURAL PREGNANCY.

Eight normotensive women who were delivered under nitrous oxide ; muscle relaxant anaesthesia showed an elevation of blood pressure of at least 20 mm.Hg. The remarkable fact is that seven were cases of normotensive plural pregnancy. Their response was of the type that the results of this investigation have come to associate with a state of increased circulatory tone.

Had these women been suffering from hypertensive toxaemia, an explanation for this occurrence would have been readily available, since there is an increased incidence of this disorder in cases of plural pregnancy, a subject ably reviewed by Bulfin and Lawler (1957). Working at the Little Company of Mary Hospital, Chicago, these clinicians

noticed that the systemic effects of the alkaloids of ergot were more pronounced in the patient whose uterus was contracting after distension from a twin pregnancy.

Sophian (1953) has long been an enthusiastic protagonist of the Trueta mechanism (Trueta et al., 1947) and the initiation of a utero-renal reflex by conditions associated with increased uterine tension. On this basis he explains the high incidence of pre-eclamptic toxaemia in patients with plural pregnancy and hydatidiform mole. According to Sophian, the utero-renal reflex is associated with the release of humoral substances by the ischaemic kidney, and these pressor substances, in turn, increase the vascular tone of the peripheral blood vessels.

On this attractive theoretical argument, it is easy to postulate that the circulation of the seven women who gave birth to twins, and who developed a hypertensive pressor response to Ergometrine, had lost its normal integrity

and assumed a state of sensitization or angiospasm. However, it is difficult to envisage the coexistance or such a circulatory state and normotension.

HYPOTENSION COINCIDING WITH ADMINISTRATION OF ERGOMETRINE.

The intravenous injection of Ergometrine in three patients with severe pre-eclampsia coincided with the development of a sudden drop in pressure of 20, 30 and 50 mm.Hg., respectively. To one woman only, methoxamine was administered with a satisfactory response. Despite the reduction in systolic pressure by 20 and 30 mm., respectively in the other two, neither received a vasopressor agent since the clinical condition of the patient did not give rise to anxiety and the dangers associated administration of a vasoconstrictor agent seemed to outweigh the advantages.

The reason for the development of the relative hypotension in these three toxaemic

women is open to argument. Before pondering over this problem, it is to be noted that not even minor degrees of hypotension occurred in any other patient in the absence of operative haemorrhage; apart from these three toxaemic women, the patients either retained their pre-ergometrine level or showed an elevation of arterial blood pressure.

Hypotension due to haemorrhage is ruled out since the loss in none was more than 10 fl. oz.

The depolarizing muscle relaxant employed throughout the series is known to affect cardiac rhythm and rate (Bullough, 1959). Sinus bradycardia, depression of the excitation and conduction of cardiac impulses, and even complete arrest may be produced by succinylcholine (Lupprian & Churchill - Davidson, 1960). The size of the incremental dose of succinylcholine and not the frequency of administration seems to be the important factor. Six out of seven patients who developed ventricular standstill in

the report by Lupprian & Churchill - Davidson, did so after a repeated dose of at least 50 mg., twice the magnitude of the increments employed during this inquiry. It may be that Ergometrine and succinylcholine, given at or about the same time, form a dangerous combination.

Was hypotension produced in the three pre-eclamptic women as a result of adrenergic blockade? It is said that compounds like Ergometrine, that do not possess a polypeptide side-chain, lack the ability of the other naturally occurring alkaloids of ergot to block and reverse the pressor effects of adrenaline and sympathetic nerve stimulation. (Goodman & Gilman, 1960). An argument against the likelihood of sympatholysis from this drug is the fact that all three patients had received thiopentone ten minutes before administration of Ergometrine, and the thiobarbiturates are known to reduce the adrenergic blocking potency of the ergot alkaloids (Goodman & Gilman, 1960).

One factor that cannot be overlooked is the

ability of ergot alkaloids to depress the myocardium directly, so reducing cardiac output. Ergot derivatives have long been known to afford protection against cardiac arrhythmias, a property supposedly due to myocardial depression.

Cases of circulatory collapse have occurred following the injection of pituitary extract during anaesthesia with certain agents, including thiopentone, and have been attributed to a combination of myocardial depression and myocardial ischaemia. That the alkaloids of ergot depress the myocardium has just been noted. It is not commonly appreciated, however, that the naturally occurring alkaloids are potent constrictors of the coronary arteries (Katz and Linder, 1939). Even at normal oxygen tensions, Ergometrine has produced anginal pain in susceptible subjects.

One cannot ignore the fact that all three patients who became relatively hypotensive presented with the clinical features of hypertensive toxaemia. In all three the raised

preoperative blood pressure was accompanied by albuminuria and widely distributed tissue oedema.

Lastly, the decline in systemic pressure could have been evidence of reflex activity, emptying of the uterus providing the afferent stimulus. Rapid evacuation or decompression of a space-occupying intra-abdominal tumour commonly evokes such a reaction. This might apply equally to evacuation of the womb at term as to rapid decompression of the urinary bladder, rupture of a large ovarian cyst, or paracentesis of an ascitic abdomen.

THE INFLUENCE OF HALOTHANE ON THE PRESSOR EFFECT OF ERGOMETRINE.

Halothane anaesthesia produces a fall in arterial pressure that is considered to be due to a combination of vasodilatation and diminution of cardiac output.

The inhalation of halothane vapour rapidly produces vasodilatation and reduction in vascular resistance that persist throughout the

period of anaesthesia (Johnstone, 1956). This vasodilatation was shown by Black and McArdle (1962) to be due to the release of vasoconstrictor tone, although the localized action of halothane on the vessel wall does play a part (Burn & Epstein, 1959). Halothane also modifies the action of noradrenaline on peripheral blood vessels.

Catecholamines influence the blood pressure not only by their action on peripheral blood vessels, but also by their effect on cardiac output, since they are liberated at the cardiac sympathetic nerve endings (Anzola & Rushmer, 1956). During halothane anaesthesia there is no compensatory increase in the secretion of adrenaline and noradrenaline (Black & McArdle, 1962) so that the heart is depressed more readily by the anaesthetic and cardiac output falls.

The fact that halothane will inhibit effectively the vasoconstrictor activity of intravenous Ergometrine has been borne out adequately by the results of the current

investigation. What has now to be determined is whether or not, as a result of these findings, the nitrous oxide, oxygen, relaxant technique of anaesthesia should now be displaced by one of the more vasodepressant forms of anaesthesia for patients suffering from hypertensive toxaemia of pregnancy.

The place of halothane in obstetrical anaesthesia has yet to be determined, despite the fact that this agent has been subjected to more experimental and clinical trial than any anaesthetic agent hitherto. This results largely from reports of extreme uterine relaxation and post-partum haemorrhage associated with its administration. That halothane is a potent relaxant of the pregnant uterus has been amply attested to by the clinical reports of MacKay (1957), Russell (1958), and Albert et al. (1959) and by the tocographic studies of Embrey et al (1959). Should this relaxation be profound, no improvement in uterine tone can be expected from injections of oxytocic posterior pituitary extract

(Albert et al., 1959) or from Ergometrine (Russell, 1958). Comfort lies, however, in the fact that on withdrawal of the anaesthetic agent, the uterine response to halothane disappears as rapidly as it occurred. It is in the face of these facts that the place of halothane has to be considered in this special situation where the circulatory effects of Ergometrine might well be a danger to the patient.

In none of the eight pre-eclamptic women anaesthetized by halothane in the present study was the level of anaesthesia profound, nor was there any obvious interference with uterine contraction and retraction, yet the depth was sufficiently adequate to afford protection from the pressor activity of the oxytocic agent. One would appear to be justified, therefore, in concluding that adequate protection is offered by a level of halothane anaesthesia insufficient to interfere with uterine retraction. Vasodilatation and reduction in vascular resistance do occur during light anaesthesia

with this fluorinated hydrocarbon (Johnstone, 1956) so that at least one definite indication for the display of halothane in obstetrical anaesthesia has been established.

MODIFICATION OF THE ERGOMETRINE EFFECT BY DI-ETHYL ETHER.

The combination of nitrous oxide, oxygen, and di-ethyl ether has long been the method of anaesthesia most commonly used for obstetrical procedures, firstly because of its safety, and secondly on account of its simplicity in the hands of the inexperienced or occasional anaesthetist. In recent years, the use of this anaesthetic method has been on the decline, for reasons that include its unpleasantness to the patient, its flammability, and its depressant effect on the foetus.

The results of the current investigation indicate that it is now time for an appraisal of the place of ether in modern obstetrical anaesthesia. In any obstetric situation

involving delivery under general anaesthesia, the technique employed by the anaesthetist must have regard not only for the nature of the maneouvre contemplated, but also for the presence of any placental pathology, for the depressant effect of anaesthetic and analgesic drugs on the foetus, and not least for any particular pathological entity in the mother. In recognition of the last of these factors, the significant depression by ether of the Ergometrine effect on the peripheral vascular bed of pre-eclamptic women might claim for this drug a better defined place in obstetrical anaesthesia.

The mechanism whereby di-ethyl ether inhibits the Ergometrine effect on arteriolar tone is not easily explained. Textbooks of anaesthesia and pharmacology (Lee, 1953 ; Adriani, 1952 ; Minnitt & Gillies, 1949) traditionally ascribe to this drug a vasodilator action, due, firstly, to depression of the smooth muscular coats of the arteriolar wall, and secondly,

to partial paralysis of the vasomotor centres. In actual fact, so many actions have been attributed to ether, as a result of some well-conducted and other less reliable animal experiments, that it is possible to invoke such explanations for circulatory changes as the occasion demands or as the investigator requires to suit his particular argument. For example, apart from the direct actions of ether on the myocardium (Prime & Gray, 1952 ; Price & Helrich, 1955), on the peripheral blood vessels (Bhatia & Burn, 1933), and on the vasomotor centres (Embley, 1902), this anaesthetic drug affects the heart rate and systemic blood pressure reflexly by increasing the sensitivity of the baroreceptors. It also causes general sympathetic stimulation through a central action on the nervous system (Elliott, 1912 ; Beattie, Brow & Long, 1930 ; Bhatia & Burn, 1933 ; Watts, 1955).

It is undoubtedly true that di-ethyl ether causes vasodilation, but the evidence in favour of the usually emphasized direct vasodepression

and medullary vasomotor paralysis as factors of importance in clinical dilatation, is scanty (Robertson, 1957). The speed with which arteriolar dilatation occurs following administration of ether anaesthesia may well be related to increased sensitivity of the baroreceptors, which has been shown to occur in light anaesthesia. Vasodilatation is most marked in the vessels of the limbs and skin and is comparatively long-lasting (Robertson, 1957).

CYCLOPROPANE AND ITS INFLUENCE ON THE ERGOMETRINE EFFECT.

The foetal blood level of cyclopropane rapidly attains and follows the maternal blood level of that drug, and since it is a profound depressant of the respiratory centres, this hydrocarbon has been unable to find popularity with obstetric anaesthetists. A second reason for its lack of popularity in this field emanates from reports of collapse and sudden death due to a combination of cyclopropane

and injections of posterior pituitary extract. (Lesser & Eason, 1954).

In the two groups of patients to whom cyclopropane was administered, the level of anaesthesia attained was light and not sufficient to interfere materially with the functions of the foetal respiratory centres. The maintenance of a light plane of anaesthesia in both series was deliberate, not merely because there was no indication for profound depth of narcosis, but primarily to explore the effect of the method on the vascular bed of toxaemic women who were receiving Ergometrine. Kitchen et al. (1953) demonstrated conclusively that the vasodilatation caused by this saturated hydrocarbon is maximal under light anaesthesia.

It has been indicated already that the scope of cyclopropane in obstetrics is largely limited to the inhalational induction of anaesthesia for extraction of the head in breech delivery. The findings in respect of its inhibition of the Ergometrine effect in pre-eclamptic women do not

compel the author to plead for an extension of the use of this drug in the treatment of such patients; halothane and di-ethyl ether are to be preferred in other forms of operative delivery. Nevertheless, it is reassuring to know that in the one form of obstetric delivery in which cyclopropane is mainly indicated, pre-eclamptic patients are not exposed to the hazards of severe rises in blood pressure resulting from the oxytocic injection.

B. PRACTICAL IMPLICATIONS.

CARDIAC DISEASE COMPLICATING PREGNANCY.

Several mechanisms, physiological, pathological and pharmacological, may cause sudden hypertension in the puerperium. Of the physiological causes, one commonly cited is the contraction and retraction of the uterine musculature, exaggerated in intensity by the action of oxytocic drugs, which results in the transfer of a large volume of blood from the uterine reservoir to the already overloaded

intravascular compartment. Doubt is cast on the importance of such a mechanism in the production of hypertension by some aspects of the current study, notably by the results of delayed injection of Ergometrine, detailed in Table VIII. Any tendency to increase the circulating blood volume must be offset partly by blood loss during parturition, particularly in operative deliveries.

Cardiac failure is a well recognised complication of heart disease in pregnancy and the mortality rate rises progressively as term is approached to reach a peak at parturition and the immediate post-partum period. (Jensen, 1938). Some deaths resulting from cardiac failure, at or about the time of delivery, have been associated with the administration of Ergometrine (Edwards et al., 1956) but the validity of the reasons given for implicating this drug are open to question. Two authors (Hoffman & Jeffers, 1942) have likened the effect on the maternal circulation of post-partum

uterine contraction to that of the rapid intravenous transfusion of blood, and, on acceptance of this principle, others (Edwards et al., 1956 ; Friedberg, 1956) have campaigned against the use of the ergot alkaloid in patients with cardiac disease. It is here contended that systemic hypertension is unlikely to occur in cardiac disease, in the absence of hypertensive toxaemia or multiple pregnancy, and that when it does present, the rise in blood pressure results largely from an increase in peripheral resistance rather than from a raised circulating blood volume.

In one of the two fatalities reported by Edwards and his associates, acute toxaemia of pregnancy was superadded to the cardiac disability; in the other, relevant details are not given.

It must be stressed, however, that the remarks made above refer to the systemic arterial circulation and not to the pulmonary circulation. During the latter months of pregnancy, the venous

return from the lower limbs is impeded by pressure of the gravid uterus on the inferior vena cava, particularly in the recumbent position. After parturition, there takes place an increase in venous return to the heart, assisted by descent of the diaphragm and the consequent decrease in mediastinal pressure (Montgomery et al., 1958). Thus there is a reasonable argument in support of pulmonary hypertension following delivery and a probable mechanism for the production of acute pulmonary oedema in women with cardiac disease, but the factors primarily concerned in their precipitation are not referable to the oxytocic activity of Ergometrine.

POST-PARTUM ECLAMPSIA.

Of pathological entities causing hypertension in the puerperium, the most important clinically is pre-eclampsia. From time to time, there appear in the literature reports of post-partum eclamptic convulsions, sometimes

in patients who had no evidence of ante-partum toxaemia (Stander et al., 1946 ; Schade, 1951 ; Hofmeister & Brown, 1953 ; Hamilton, 1953 ; McFadyen, 1960).

Post-partum eclampsia, of course, was a recognised clinical hazard in days preceding the widespread intravenous administration of Ergometrine maleate, but the fact that this drug is capable of evoking an elevation in blood pressure of up to 46 mm.Hg. in pre-eclamptic women cannot be ignored as a possible contributing factor in the precipitation of fits in such patients.

Spasm of small blood vessels is an important feature of the entire disease process of toxaemia of pregnancy and, whether it is the fundamental pathological basis or merely a secondary manifestation of the disease, the fact remains that in this condition the vascular bed is in a state of sensitization and readiness for the production of an additive and intense vasoconstrictor response to Ergometrine.

Ergometrine maleate appears to act in a synergistic manner on the peripheral blood vessels when given with a vasopressor substance, whether that substance be a pharmacological agent such as methoxamine, or a physiological one such as pituitrin or the pressor substance of pre-eclampsia. Just as the cumulative effect of the ergot alkaloid and vasopressor drugs may be out of proportion to the expected reaction from individual injection of either, so the vasoconstrictor response to Ergometrine in the pre-eclamptic patient might be sufficiently intense to precipitate an eclamptic seizure.

There would seem to be a fair amount of evidence to support a plea for the use of smaller doses of Ergometrine in patients with toxaemia of pregnancy. The post-partum uterus is extremely sensitive to action of this alkaloid, positive effects having been produced with less than 0.05 mm. intravenously (Smith, 1938). 0.2 mg., has been described as the

optimal intravenous dose (Adair et al., 1935) and is that commonly employed in centres in the United States of America. In Moir's (1944) opinion, an amount of 0.25 mg., should never be exceeded by intravenous injection.

Observation of patients under the narcotic influence of tribromethanol, suggests that this alcohol protects severely toxaemic patients from the vasopressor response to Ergometrine. One such patient occurred in the current investigation and the results obtained in her case have been substantiated by my recent observation of the effect of the oxytocic drug on three women under tribromethanol narcosis, who did not require general anaesthesia for delivery. The apparent protection offered by this basal narcotic results from its two-fold action on the circulatory system, firstly depression of the vasomotor centres in the medulla, and secondly relaxation of the walls of the smaller blood vessels (Lee, 1953).

INTRACRANIAL HAEMORRHAGE.

Cassady et al (1960) have given fresh emphasis to the risk of subarachnoid and intracerebral haemorrhage in hypertensive women and in their recent paper cited nine cases of post-partum hypertension with cerebral haemorrhage following injection of a vasopressor agent, an oxytocic drug, or a combination of the two. Included in their review of post-partum cerebral catastrophies was the case report of one of their own patients who had a subarachnoid haemorrhage from a ruptured intracranial aneurysm within two hours of delivery. Delivery in this case was effected under caudal epidural analgesia, and to counteract any tendency towards hypotension as a result of the block, methoxamine 10 mg. was administered. At the time of placental delivery, 0.23 mg. Ergometrine maleate was given, whereupon the systemic blood pressure rose from 120/76 mm. to 180/120 mm.Hg., and at that pressure rupture of the aneurysm occurred.

The additional influences on the blood

pressure of psychomotor activity and voluntary movement might well render the Ergometrine effect a greater hazard to conscious than to unconscious patients. Certainly, these two and other factors cause wide variations in the pattern of blood pressure when hypertensive patients recover from general anaesthesia. Personal observation has been made of the influence of certain phenothiazine derivatives and on environmental and bed temperatures on these women (Baillie, 1962). In recent years it has been the practice to return patients from the operating suite to a cool bed in order to avoid peripheral vasodilation and hypotension. Here is an indication for reversal of that general rule and the application of moderate warmth.

ACCIDENTAL HAEMORRHAGE.

Obstetricians not uncommonly experience anxiety over the suppression of urinary secretion in patients suffering from accidental haemorrhage.

Although the cause of the renal tubular damage associated with concealed accidental haemorrhage is still unknown, it is believed that damage to uterine muscle fibres releases myoglobin into the circulation. This, possibly in association with shock, causes constriction of the renal vessels, in particular the arterioles supplying the tubules. Should this arteriolar spasm persist unduly long, therefore, tubular damage or even necrosis will ensue.

One is led to wonder how great or significant effect the administration of Ergometrine exerts on such renal angiospasm. It is always difficult to translate the inferences of animal experiments in terms of clinical effects on human beings, but the fact that Ergometrine does constrict the renal arteriolar vessels in the experimental animal (Hamet, 1935), cannot be ignored. In the absence of more precise knowledge of the influence of this oxytocin agent on the blood vessels of the human kidney during pregnancy, it is probably wise to concur with Byrom and Pratt (1962)

who state that in this connection, all potential vasoconstrictors must be suspect.

SELECTION OF ANAESTHESIA.

Since most forms of conduction anaesthesia are regarded as unsuitable for obstetrical emergency procedures (Kingson & Kellman, 1956 ; Apgar et al., 1957 ; Crawford, 1959), general anaesthesia is required for the greater number of operative deliveries.

The selection of a particular general anaesthetic technique, however, is not a simple one, since a great number of factors must influence the ultimate choice. As in the provision of anaesthesia for general surgical procedures, the physical condition of the patient, the specific pathological process demanding surgical intervention, the type and site of operation envisaged, and any particular vagaries of the surgeon have to be catered for. Application of these factors alone to obstetrical anaesthesia, whilst providing pleasant and safe anaesthesia

for the mother and ideal operating conditions for the obstetrician, might nevertheless inflict untold harm on the foetus. Thus, in anaesthesia for any obstetrical maneouvre that is likely to culminate in delivery of the infant, further consideration must take into account the ease of placental transmission of the narcotic drugs used and their action on the foetal medullary respiratory mechanism, especially in the presence of foetal distress or prematurity.

Evaluation of different anaesthetic sequences must be carried out in the light of these latter, foetal factors. In consequence, some acceptable means of assessing the viability of babies delivered under the various methods of narcosis is necessary. This is provided quite conveniently by calculation of the Apgar score (Apgar, 1953), or even more simply by estimation of the delivery - breathing and delivery - crying times (Hodges et al., 1959).

By employing the latter method, Hodges,

Bennett and Tunstall (1959) compared the effects on the foetus of four anaesthetic techniques: thiopentone, succinylcholine, nitrous oxide and oxygen, cyclopropane and oxygen, nitrous oxide, oxygen and ether, and nitrous oxide, oxygen and trichlorethylene.

The absence of foetal depression in babies whose mothers were anaesthetized by the first of these sequences, was so outstanding that, wherever a specialist anaesthetic service is available, the nitrous oxide muscle relaxant method has won for itself universal adoption.

The theme of this thesis, however, suggests that this form of anaesthesia is not a suitable one for women presenting with the clinical features of acute toxaemia of pregnancy, in view of the significant incidence of hypertension that follows intravenous administration of Ergometrine in such cases.

Whilst there may be a case for the use of a smaller dose of the oxytocic drug in the presence of hypertensive toxaemia, there is

nevertheless contained in the results of the present study, a challenge to cater for yet another aspect of obstetrical anaesthesia.

Halothane, di-ethyl ether and cyclopropane have all been shown to modify the pressor response to Ergometrine. Their acceptability, therefore, depends on the ratio of their capacity to inhibit the Ergometrine effect to their depressant effect on the foetus.

The recent introduction of the fluorinated hydrocarbon, halothane, into anaesthetic practice, resulted inevitably in the exploration of its possible virtues in obstetrics. Montgomery (1961), in a comparison of the Apgar scores (Apgar, 1953) of infants born by Caesarean section using the Hodges technique and of those delivered by the same operation employing a halothane anaesthesia, demonstrated that halothane given in a concentration of I - 2% (i.e. vaporizer concentration) was much more depressant to the newborn than nitrous oxide and oxygen in combination with succinylcholine. The scores

obtained by Montgomery in respect of halothane closely paralleled those of Apgar (1953) using cyclopropane, and from the foetal point of view, therefore, there seems to be little to choose between the two.

Over and above its depressant effect on the foetal medulla, halothane is a potent relaxant of the gravid uterus (MacKay, 1957 ; Russell, 1958 ; Albert et al., 1959 ; Embrey et al., 1959), and to the hazards attendant on the latter action, reference has been made already. It has been stated, therefore, (Crawford, 1962) that the exhibition of halothane should be limited to cases requiring uterine relaxation, e.g. external cephalic version when uterine hypertonicity is impeding the manipulation, acute inversion of the uterus, and operative difficulties associated with constriction ring formation.

In the author's opinion, however, the scope of this useful fluorinated hydrocarbon must be broadened to include anaesthesia for pre-eclamptic

women. Profound depth of narcosis, sufficient to interfere with retraction and contraction of the uterus is unnecessary to inhibit the Ergometrine effect since even light halothane anaesthesia produces marked peripheral vasodilation (Johnstone, 1956). Even before the level of blood pressure starts to decline, vasodilatation is in evidence, the maintenance of pressure being attributable to an increase in cardiac output at this light plane (Black and McArdle, 1962).

The enthusiastic reports concerning the use of halothane in obstetrical anaesthesia (Brown and Woods, 1958 ; Sheridan and Robson, 1959), tend to suggest that, as with so many other types of therapy, the man is more important than the method.

With regard to cyclopropane, a degree of foetal medullary depression comparable with that of halothane has been noted. Largely for this reason, trimethylene has been almost abandoned in this country as an anaesthetic agent for

operative obstetrics. Reference has been drawn to its value in the provision of anaesthesia for delivery of the after-coming head in assisted breech delivery. In this situation, administration of cyclopropane coincides with a point in parturition at which placental transmission ceases and the main argument against the display of the drug is not relevant. Routine assessment of all newborn infants by the Apgar system is employed by the author, and this latter statement concerning cyclopropane is supported by the fact that in all breech deliveries occurring in the current study, the score at I minute was IO.

Hodges, Bennett and Tunstall (1959) demonstrated a marked contrast in viability between babies born after the display of nitrous oxide : muscle relaxant anaesthesia and after ether anaesthesia. Whereas newborn infants of the former group were hardly affected, the incidence of neonatal respiratory depression following ether techniques was very high, more

so than after trimethylene or trichlorethylene sequences.

There are probably few indications for the exhibition of ether in an obstetric unit that boasts of a specialist anaesthetic service. In consideration of the incidence of foetal depression following ether anaesthesia, a very good case must exist for display of this agent when the operation is likely to culminate in delivery of the baby. It is believed that the existence of maternal pre-eclampsia is such an indication. In this connection, it is to be stressed that, in order to inhibit the pressor effect of Ergometrine, vaporization of ether need not commence until delivery is imminent. In this way, not only is maternal safety guaranteed, but the occurrence of foetal depression is unlikely.

The vasodilatation that results from inhalation of di-ethyl ether tends to persist for some considerable time after termination of the anaesthesia (Robertson, 1957). This

particular attribute might be expected, therefore, to protect the patient during the immediate post-anaesthetic period until the tendency to react to Ergometrine has passed off.

The number of drugs that exert their main pharmacological action, without at the same time producing undesirable side-effects, must be very small and Ergometrine certainly cannot be included among them. Nevertheless, it must be stressed that, as well as being an agent that holds potential dangers for patients whose vasoconstrictor mechanism has been sensitized by administration of a vasopressor agent or by the presence of pre-eclamptic toxaemia, Ergometrine has been shown by the results of this inquiry to be a remarkably safe drug for administration to normotemsive women and to those suffering from chronic hypertensive cardiovascular disease. It would be wrong, therefore, to conclude this discussion without stating that the findings of this investigation in no way call for any

modification of the routine administration of Ergometrine to normotensive women who, after all, form the greater number of our patients.

CONCLUSIONS.

CONCLUSIONS.

In a study of pregnant patients who required general anaesthesia for operative or instrumental delivery, 0.5 mg. Ergometrine maleate was given intravenously as an oxytocic agent following delivery of the child, and the circulatory response observed. As a result of this investigation it is concluded that:-

(1) Ergometrine does not evoke a significant vasopressor response in normotensive women after delivery of a single foetus,

(2) women who give birth to twins are likely to show an elevation of blood pressure after intravenous administration of the drug,

(3) a marked rise in systolic and diastolic blood pressures, in many cases exceeding 20 mm.Hg., is the general rule in patients suffering from hypertensive toxaemia of pregnancy,

(4) when ante-natal hypertension is due

to established chronic vascular disease, there is no danger associated with the administration of Ergometrine,

(5) Modern techniques of anaesthesia that preserve the integrity of the vasoconstrictor mechanism, offer no protection from the vasopressor activity of this oxytocic drug. In this respect, vasodepressant techniques employing di-ethyl ether, halothane, or cyclopropane have been shown to have a definite inhibitory effect on the pressor response,

(6) The papaverine - like effect attributed to pethidine is too weak to counteract the hypertensive action of Ergometrine,

(7) Hypertension during labour is not an index of the possibility of occurrence of the Ergometrine effect. Only the basal level of blood pressure has been established as having any significant relationship to the

circulatory response.

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APPENDICES.

APPENDIX A.

VASOPRESSOR EFFECT OF ERGOMETRINE BLOOD PRESSURE READINGS IN 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
1.	29.	105/60	120/84	4/2	
2.	27.	110/60	150/94	0/0	
3.	31.	100/65	108/70	0/4	
4.	34.	100/65	160/118	6/0	
5.	28.	105/65	152/128	2/0	
6.	40.	110/65	120/75	0/0	
7.	39.	115/65	130/86	0/0	
8.	23.	125/65	128/76	10/6	
9.	21.	100/66	146/104	0/0	
10.	26.	110/66	144/112	16/10	
11.	26.	112/68	140/90	0/4	
12.	24.	120/70	120/94	0/0	
13.	41.	100/70	122/86	0/0	
14.	27.	100/70	110/76	0/0	
15.	20.	100/70	110/74	0/0	

APPENDIX A (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE BLOOD PRESSURE READINGS IN 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
16.	24.	100/70	130/92	0/0	
17.	32.	100/70	116/84	0/0	
18.	36.	105/70	120/86	0/0	
19.	25.	105/70	154/108	0/0	
20.	28.	105/70	130/92	0/0	
21.	33.	106/70	132/114	8/2	
22.	22.	110/70	124/88	6/4	
23.	29.	110/70	160/96	0/0	
24.	24.	110/70	90/66	0/0	
25.	40.	110/70	150/94	0/0	
26.	40.	110/70	110/72	0/0	
27.	32.	110/70	118/70	0/0	
28.	28.	110/70	128/84	0/0	
29.	26.	110/70	110/70	0/0	
30.	41.	110/70	138/90	2/2	

APPENDIX A (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE BLOOD PRESSURE READINGS IN 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
31.	42.	110/70	124/82	0/0	
32.	28.	110/70	100/70	0/0	
33.	22.	110/70	110/70	0/0	
34.	25.	110/70	158/116	0/0	
35.	37.	110/70	134/76	6/4	
36.	31.	110/70	100/70	0/0	
37.	21.	110/70	110/80	0/0	
38.	42.	110/70	110/70	0/0	
39.	27.	110/70	136/102	12/10	
40.	21.	110/70	136/102	12/10	
41.	25.	114/70	116/70	0/0	
42.	30.	114/70	132/86	2/0	
43.	28.	114/70	138/96	0/0	
44.	36.	114/70	114/70	6/10	
45.	31.	115/70	138/94	0/0	

APPENDIX A (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE BLOOD PRESSURE READINGS in 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
46.	23.	115/70	136/106	0/0	
47.	33.	115/70	114/70	0/0	
48.	27.	115/70	142/98	0/0	
49.	32.	120/70	164/100	0/0	
50.	24.	120/70	120/70	0/2	
51.	20.	120/70	140/82	4/0	
52.	40.	120/70	110/70	4/0	
53.	31.	120/70	140/84	0/4	
54.	20.	120/70	132/80	0/0	
55.	27.	120/70	166/122	0/0	
56.	28.	120/70	120/76	0/4	
57.	30.	120/70	166/120	0/0	
58.	41.	120/70	142/80	0/0	
59.	22.	125/70	130/70	0/0	
60.	26.	126/70	120/72	0/0	
61.	41.	130/70	140/84	0/0	

APPENDIX A (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE BLOOD PRESSURE READINGS in 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal Bp mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
62.	24.	100/72	120/80	0/0	
63.	25.	124/72	170/124	0/0	
64.	27.	110/74	114/76	4/4	
65.	39.	120/74	130/80	10/6	
66.	41.	120/74	182/124	2/0	
67.	32.	126/74	164/120	0/0	
68.	31.	105/75	118/84	12/6	
69.	31.	110/75	140/94	42/8	Twin Pregnancy.
70.	26.	110/75	140/82	0/0	
71.	21.	120/75	162/116	0/0	
72.	20.	120/75	120/85	0/0	
73.	29.	120/75	142/100	0/0	
74.	30.	125/75	110/74	16/16	
75.	18.	108/76	150/100	10/4	
76.	38.	110/76	120/80	0/0	

APPENDIX A (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE BLOOD PRESSURE READINGS in 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
77.	20.	110/76	128/86	26/18	Twin Pregnancy.
78.	29.	110/76	110/76	0/0	
79.	23.	114/76	110/76	0/0	
80.	38.	118/76	126/90	4/0	Twin Pregnancy.
81.	22.	120/76	132/86	8/4	
82.	21.	120/76	120/74	4/2	
83.	40.	124/76	124/88	4/2	
84.	32.	124/76	144/106	0/0	
85.	33.	130/76	150/96	0/2	
86.	29.	100/78	140/100	0/0	
87.	45.	140/78	134/98	60/50	
88.	43.	102/80	158/126	92/20	Syntocinon Drip.
89.	26.	105/80	104/78	0/0	
90.	26.	110/80	112/80	12/10	
91.	37.	110/80	160/118	0/0	
92.	26.	110/80	126/88	2/2	

APPENDIX A (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE BLOOD PRESSURE READINGS IN 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
93.	29.	110/80	128/100	2/0	
94.	32.	110/80	110/74	0/0	
95.	23.	110/80	110/80	0/0	
96.	23.	110/80	116/86	0/0	
97.	29.	110/80	114/82	0/0	
98.	32.	110/80	156/104	2/0	
99.	20.	110/80	110/74	0/0	
100.	25.	110/80	110/70	26/8	Twin Pregnancy.
101.	28.	115/80	130/92	10/4	
102.	24.	115/80	134/100	4/0	
103.	19.	116/80	136/98	10/8	
104.	26.	116/80	130/94	20/14	Twin Pregnancy.
105.	34.	118/80	140/104	34/18	Twin Pregnancy.
106.	38.	118/80	120/80	4/0	
107.	33.	120/80	134/102	0/0	
108.	24.	120/80	140/92	0/0	

APPENDIX A (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE BLOOD PRESSURE READINGS IN 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
109.	32.	120/80	158/106	12/8	
110.	23.	120/80	130/86	10/6	
111.	23.	120/80	146/114	6/4	
112.	35.	120/80	110/74	0/0	
113.	33.	120/80	120/84	16/12	
114.	35.	120/80	124/84	6/2	
115.	27.	120/80	130/86	0/0	
116.	38.	120/80	120/80	0/0	
117.	30.	120/80	120/86	6/2	
118.	35.	120/80	124/80	0/0	
119.	33.	120/80	160/104	0/4	
120.	40.	120/80	180/108	0/0	
121.	42.	120/80	140/92	0/0	
122.	33.	120/80	126/84	0/2	
123.	26.	120/80	136/86	4/0	

APPENDIX A (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE BLOOD PRESSURE READINGS IN 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
124.	30.	120/80	146/110	0/0	
125.	21.	120/80	120/80	0/0	
126.	21.	120/80	120/80	0/0	
127.	28.	120/80	110/66	0/0	
128.	23.	120/80	140/100	0/0	
129.	21.	120/80	130/92	0/0	
130.	32.	120/80	110/80	10/4	
131.	38.	120/80	144/112	26/26	Oedema and Albuminuria.
132.	21.	120/80	108/70	0/0	
133.	25.	120/80	130/84	0/0	
134.	23.	120/80	146/110	0/0	
135.	38.	124/80	120/82	0/2	
136.	19.	124/80	140/120	6/0	
137.	23.	124/80	130/90	0/0	
138.	27.	124/80	146/120	6/0	
139.	25.	125/80	116/76	4/4	

APPENDIX A (continued).

VASOPRESSOR EFFECT OF ERGOMATRINE BLOOD PRESSURE READINGS IN 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
140.	32.	125/80	160/84	10/6	
141.	29.	125/80	124/92	2/0	
142.	34.	126/80	140/86	0/0	
143.	36.	126/80	168/114	0/0	
144.	25.	126/80	180/114	0/0	
145.	17.	126/80	130/86	14/8	
146.	21.	130/80	160/124	12/6	Twin Pregnancy.
147.	22.	130/80	138/110	6/0	
148.	39.	130/80	160/124	0/0	
149.	23.	130/80	140/84	0/0	
150.	15.	130/80	120/76	10/2	
151.	26.	130/80	130/92	0/0	
152.	21.	130/80	146/88	14/10	
153.	29.	140/80	140/80	6/4	
154.	28.	130/82	140/94	0/0	
155.	22.	120/84	132/86	2/0	

APPENDIX A (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE BLOOD PRESSURE READINGS IN 169 NORMOTENSIVE WOMEN UNDER NITROUS OXIDE, OXYGEN, RELAXANT ANAESTHESIA.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
156.	24.	120/84	164/120	2/0	
157.	37.	120/84	130/90	0/0	
158.	25.	120/84	142/108	4/8	
159.	21.	120/84	158/100	0/0	
160.	20.	120/84	136/96	0/0	
161.	41.	126/84	184/128	0/0	
162.	20.	130/84	152/118	0/0	
163.	23.	110/85	134/98	0/2	
164.	20.	110/85	126/92	0/0	
165.	26.	115/85	132/96	2/0	
166.	19.	120/85	134/94	4/4	
167.	36.	110/86	166/130	4/4	
168.	19.	118/86	124/94	2/0	
169.	23.	128/88	156/120	0/0	

APPENDIX B.

VASOPRESSOR EFFECT OF ERGOMETRINE MALEATE - READINGS OF BLOOD PRESSURE IN 53 WOMEN WITH BASAL DIASTOLIC PRESSURE OF 90 - 99 mm.Hg. AND ANAESTHETIZED BY NITROUS OXIDE, OXYGEN, RELAXANT TECHNIQUE.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
1.	30.	120/90	104/86.	26/16	Severe Hydramnios.
2.	29.	120/90	100/70.	0/0	
3.	20.	120/90	110/86	0/0	
4.	25.	120/90	150/102	14/18	
5.	33.	120/90	110/86	4/4	
6.	29.	122/90	108/80	0/0	
7.	21.	126/90	136/108	6/12	
8.	33.	126/90	130/98	10/8	
9.	23.	130/90	126/90	4/2	
10.	37.	130/90	130/92	10/10	
11.	25.	130/90	146/100	6/4	
12.	21.	130/90	130/90	0/0	Syntocinon Drip.
13.	22.	130/90	140/94	0/4	
14.	28.	130/90	128/90	12/4	

APPENDIX B (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE MALEATE - READINGS OF BLOOD PRESSURE IN 53 WOMEN WITH BASAL DIASTOLIC PRESSURE OF 90 - 99 mm.Hg. AND ANAESTHETIZED BY NITROUS OXIDE, OXYGEN, RELAXANT TECHNIQUE.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
15.	20.	130/90	120/88	0/2	
16.	18.	130/90	168/114	0/0	
17.	36.	130/90	146/98	4/4	Renal Glycosuria.
18.	23.	130/90	126/90	10/6	
19.	21.	130/90	140/106	10/4	
20.	37.	130/90	170/126	0/0	Diabetic.
21.	36.	130/90	140/94	16/10	
22.	41.	130/90	140/96	16/8	
23.	30.	130/90	124/76	18/10	
24.	17.	130/90	146/114	18/10	
25.	25.	135/90	140/92	16/10	
26.	42.	140/90	118/74	20/14	
27.	19.	140/90	138/90	8/0	
28.	39.	140/90	134/90	18/8	
29.	23.	140/90	126/96	18/4	

APPENDIX B (CONTINUED).

VASOPRESSOR EFFECT OF ERGOMETRINE MALEATE - READINGS OF BLOOD PRESSURE IN 53 WOMEN WITH BASAL DIASTOLIC PRESSURE OF 90 - 99 mm.Hg AND ANAESTHETIZED BY NITROUS OXIDE, OXYGEN, RELAXANT TECHNIQUE.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
30.	31.	140/90	154/116	4/6	
31.	33.	140/90	130/90	10/10	
32.	35.	140/90	158/118	12/16	
33.	25.	150/90	180/146	16/4	
34.	28.	150/90	150/88	22/20	
35.	38.	156/90	142/84	10/4	Chronic Hypertension.
36.	32.	120/92	146/110	0/0	
37.	30.	130/94	152/106	16/10	
38.	25.	130/94	138/96	10/8	
39.	24.	132/94	160/118	10/10	
40.	23.	130/95	120/92	14/12	
41.	24.	135/95	150/90	30/20	Twin Pregnancy.
42.	22.	140/95	156/108	BP fell to 126/84 mm.Hg.	
43.	24.	145/95	180/116	0/0	Chronic Nephritis.

APPENDIX B (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE MALEATE - READINGS OF BLOOD PRESSURE IN 53 WOMEN WITH BASAL DIASTOLIC PRESSURE OF 90 - 99 mm.Hg. AND ANAESTHETIZED BY NITROUS OXIDE, OXYGEN, RELAXANT TECHNIQUE.

Identification	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
44.	37.	145/95	164/116	46/24	
45.	40.	150/95	168/118	2/0	Chronic Hypertension.
46.	29.	150/95	144/90	20/10	
47.	23.	155/95	150/96	30/24	
48.	30.	130/96	130/96	18/8	
49.	28.	134/96	164/120	10/10	
50.	18.	140/96	140/96	14/10	
51.	22.	140/96	164/138	16/14	
52.	38.	148/96	176/134	0/0	Chronic Hypertension.
53.	40.	140/98	140/100	BP fell	to 90/60 mm.Hg.

APPENDIX C.

VASOPRESSOR EFFECT OF ERGOMETRINE MALEATE - READINGS OF BLOOD PRESSURE IN 31 WOMEN WITH BASAL DIASTOLIC PRESSURE OF 100 mm.Hg. OR MORE, AND ANAESTHETIZED BY NITROUS OXIDE, OXYGEN, RELAXANT TECHNIQUE.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
1.	21.	130/100	120/98	40/24	
2.	26.	140/100	160/114	10/6	
3.	18.	140/100	170/118	0/2	Syntocinon Drip.
4.	31.	140/100	140/100	40/24	
5.	22.	140/100	148/98	18/10	
6.	18.	140/100	104/72	40/26	
7.	23.	140/100	140/100	30/22	
8.	24.	146/100	176/122	20/24	
9.	31.	150/100	140/100	20/8	
10.	27.	150/100	140/100	20/14	
11.	25.	150/100	160/100	20/10	
12.	37.	160/100	160/100	36/26	
13.	37.	160/100	160/112	12/6	Chronic Hypertension.
14.	32.	130/104	150/110	10/4	
15.	23.	160/105.	130/86	36/26	

APPENDIX C (continued).

VASOPRESSOR EFFECT OF ERGOMETRINE MALEATE - READINGS OF BLOOD PRESSURE IN 31 WOMEN WITH BASAL DIASTOLIC PRESSURE OF 100 mm.Hg. OR MORE, AND ANAESTHETIZED BY NITROUS OXIDE, OXYGEN, RELAXANT TECHNIQUE.

Identification Number.	Age.	Basal BP mm.Hg.	BP before Ergometrine mm.Hg.	Rise 3 mins. after I.V. Ergometrine mm.Hg.	Remarks.
16.	29.	130/106	146/116	14/10	Twin Pregnancy.
17.	37.	150/106	198/150	8/4	Chronic Hypertension.
18.	44.	160/108	184/116	6/0	Chronic Hypertension.
19.	39.	160/108	198/128	2/2	Chronic Hypertension.
20.	30.	148/110	150/122	20/12	
21.	22.	150/110	154/110	28/20	
22.	21.	165/110	170/120	BP fell to 150/106 mm.Hg.	
23.	35.	170/110	164/110	0/0	
24.	34.	180/110	180/100	20/10	
25.	23.	180/110	120/82	40/30	
26.	30.	200/110	150/108	40/28	
27.	36.	144/116	184/134	0/0	Chronic Hypertension.
28.	42.	190/116	144/96	0/0	Chronic Hypertension.
29.	30.	150/120	150/118	6/0	Chronic Hypertension.
30.	27.	150/120	154/124	0/0	Twin Pregnancy under tribromethanol narcosis.
31.	39.	220/135	184/106	4/0	Chronic Hypertension.